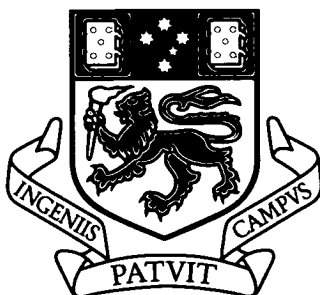


New synthetic approaches to indolizidine and pyrrolidine alkaloids



UNIVERSITY
OF TASMANIA

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of the degree Doctor of Philosophy

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Declaration:

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, and to the best of my knowledge contains no material previously published or written by another person, except where due acknowledgement is made in the text.



Brendon Gourlay,

January 2010.

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Abstract:

This thesis describes synthetic approaches towards indolizidine and pyrrolidine alkaloids.

The total synthesis of indolizidine 167B, and its *epi*-analogue was achieved from D-norvaline, which was converted to an α -pyrrolic ester through a refined Clauson-Kaas pyrrole synthesis. The method was developed by investigating the reaction requirements for pyrrole synthesis, and it was found that a two-step, one pot procedure is far superior to current methods. Chain homologation gave the γ -pyrrolic analogue, which underwent cyclisation to form the 5-propyl-6,7-dihydro indolizin-8(5*H*)-one core, which represented a formal synthesis of (-)-indolizidine 167B. An alternate reduction strategy of this derivative was developed using a dissolving metal reduction, which allowed access to *epi*-indolizidine 167B, allowing synthesis of both diastereomers from a common intermediate. This research was extended to the synthesis of higher homologues of the 5-alkyl indolizidines by using homoserine as the starting material. Pyrrole formation, chain homologation and mesylation gave an intermediate which was elaborated to give a formal synthesis of indolizidine 209D through cuprate chemistry.

The synthesis of pyrrolidine alkaloids was also investigated using a [3+2] azomethine ylide cycloaddition as the ring-forming step. Investigation into diastereoselective pyrrolidine synthesis through lithium bromide mediated generation of stabilised azomethine ylides from imines and subsequent cycloaddition showed a lack of reactivity. Therefore pyrrolidine formation was achieved by *in situ* generation of a non-stabilised ylide through decarboxylation and subsequent cycloaddition with a dipolarophile. The non-stabilised ylide formed from *N*-methyl alanine and anisaldehyde underwent cycloaddition with 1,2-*trans*-bisphenylsulfonyl ethylene to give a pyrrolidine in a three component coupling reaction. Reductive desulfonation, epoxidation and ring-opening then yielded a C3-C4 *cis* diol isomer of the alkaloid codonopsinine. A formal synthesis of (\pm)-codonopsinine was also achieved from *N*-benzyl alanine.

The azomethine ylide chemistry was further elaborated with the use of the chiral dipolarophile (-)-8-phenylmenthyl acrylate allowing the formal synthesis of β -proline.

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Lastly, thanks to my family for their unconditional love and support, particularly my wife Jen to whom I dedicate this thesis.

Abbreviations:

Bn	benzyl
CBZ	benzyloxycarbonyl
Bu ⁿ	<i>n</i> -butyl (CH ₂ CH ₂ CH ₂ CH ₃)
Boc	<i>t</i> -butyl carbamate
TBS	<i>t</i> -butyldimethylsilyl
cat.	catalytic
<i>m</i> -CPBA	3-chloroperbenzoic acid
CSIRO	Commonwealth Scientific and Industrial Research Organisation
°C	degrees Celsius
dr	diastereomeric ratio
DBU	1,8-diazabicycloundec-7-ene
DIBAL-H	di-isobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
ee	enantiomeric excess
Et	ethyl (CH ₂ CH ₃)
eq	equivalent(s)
GC	gas chromatography
h	hour(s)
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectroscopy
IR	infrared
LUMO	lowest unoccupied molecular orbital
Me	methyl (CH ₃)
μwave	microwave
min	minute(s)
Ms	mesyl (methanesulfonyl)

NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
<i>p</i> -tol	4-methylphenyl (<i>para</i> -tolyl)
ppm	parts per million
psi	pounds per square inch
r.t.	room temperature
SAR	structure activity relationship
THF	tetrahydrofuran
PhMe	toluene
Ts	tosyl (toluenesulfonyl)
OTf	triflate (trifluoromethanesulfonate)
TFA	trifluoroacetic acid
TMS	trimethylsilyl

List of Publications:

Gourlay, B. S.; Little, I.; Ryan, J. H.; Smith, J. A. *Natural Product Communications* **2006**, *1*, 831-837.

Gourlay, B. S.; Molesworth, P. P.; Ryan, J. H.; Smith, J. A. *Tetrahedron Letters* **2006**, *47*, 799-801.

Gourlay, B. S.; Ryan, J. H.; Smith, J. A. *Beilstein Journal of Organic Chemistry* **2008**, *4*.

Chapter 1: Indolizidine Chemistry

1.1 Introduction to indolizidines

Indolizidine alkaloids ('indolizidines') are a major class of azabicyclic natural products that are characterised by their octahydroindolizine skeleton (**1**) (Figure 1).

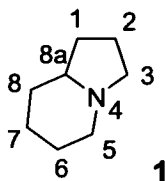


Figure 1: Indolizidine skeleton. The convention used for numbering is shown.

Indolizidine alkaloids have been isolated from numerous natural sources such as plants,^{1,2} frogs³ and ants.⁴ A major group within indolizidines are the alkyl-substituted indolizidines. The most well known source of alkyl indolizidines are the “poison arrow” frogs, *Dendrobatidae*,^a from South America. Daly's 2005 review gives a thorough overview of alkaloids extracted from amphibian skins, and estimates that over 800 such alkaloids have been identified.³ Of these alkaloids, indolizidines represent a major structural class, within excess of 200 examples known. Many types of substitution patterns have been discovered including the 3,5-disubstituted, 5,8-disubstituted and 5,6,8-trisubstituted indolizidine derivatives.

As well as a good variety of substitution patterns around the bicyclic ring, the stereochemistry of the substituents also differs. This is highlighted by indolizidines 195B (**2**) and 223AB (**3**), both 3,5-disubstituted indolizidines, where all four possible diastereomers have been identified from *anuran* skin extracts (Figure 2).³

^a *Dendrobatidae* are a family of frogs belonging to the order *anura* of the *amphibian* class of the animal kingdom.⁵

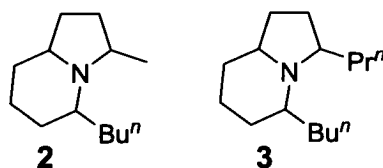


Figure 2: Examples of indolizidines where all four possible diastereomers have been isolated.

The alkyl indolizidines have garnered the interest of synthetic organic chemists due to their biological activity. The activity of these alkaloids is thought to be primarily due to their action as non-competitive antagonists of nicotinic receptors and has been comprehensively reviewed by Daly.⁵ The lack of access to natural sources means that total synthesis is required for further biological evaluation and preparation of more active analogues.

On many occasions the total synthesis of alkyl indolizidines has been required for proof of structure studies. This is highlighted by two natural products that were initially proposed to have 5-substituted indolizidine structures, 167B (**4**) and 209D (**5**) (Figure 3), but whose structures were later corrected. The natural products were obtained in trace amounts from the skins of frog species found in a single population on the Isla de Colon, Panama,⁶ and due to the small amounts of each alkaloid isolated the structural assignment was dependent on mass-spectral fragmentation patterns. Later synthesis of the proposed structures led to a revision for the structure of the natural products, to their 3-methyl pyrrolizidine analogues **4a** and **5a**.³ This reassignment highlights the importance of total synthesis in confirmation of the structure of natural products that are not available from their environmental source.

In the case of alkaloids from the “poison arrow” frogs, the problem of the lack of availability of natural sources of the compounds was further reinforced when the Convention on International Trade in Endangered Species (CITES) listed all Dendrobatidae species on its Appendix II register, meaning that collection of these species is now prohibited. Attempts have been made to breed the frogs in captivity; however no trace of alkaloids was

detected.^{7,8} This effect was also shown when frogs of the same species were collected from different habitats and were found to contain differing quantities and types of alkaloids. Thus, evidence suggests the frogs sequester the alkaloids from their arthropod prey. To test this hypothesis, Daly performed a series of feeding experiments to determine if the frogs could sequester alkaloids through their diet, feeding captive raised frogs a known source of the indolizidine (+)-monomorine (**6**), a trail pheromone from the Pharaoh ant (*Monomorium pharaonis*) (Figure 3). The tests were successful and the frogs accumulated the indolizidine in high concentrations.

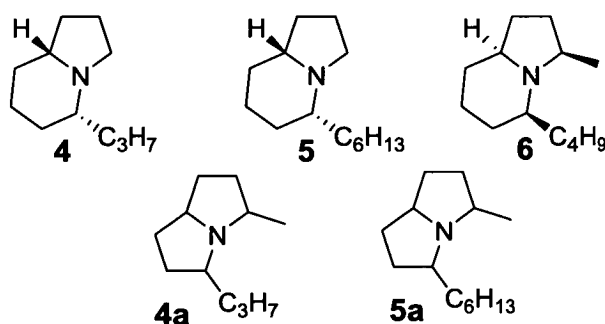


Figure 3: Indolizidine alkaloid examples.

Saporito *et al.* have recently published a review⁹ of studies that have provided evidence for a dietary source for the “poison arrow” frog alkaloids, as well as outlining current investigations aimed at identification of the dietary sources of all alkaloids present in the “poison arrow” frogs.

The other major group of biologically important indolizidine alkaloids is the polyhydroxylated indolizidines, typified by the best known examples, castanospermine (**7**) and swainsonine (**8**), (Figure 4).

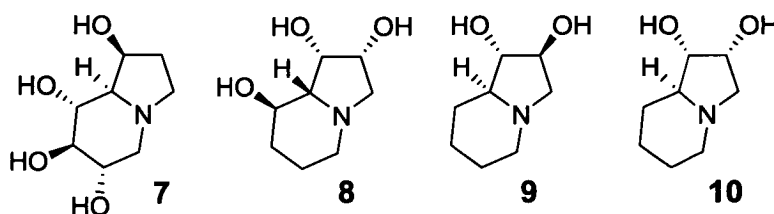


Figure 4: Hydroxylated indolizidine alkaloids.

Castanospermine (**7**) was originally isolated in Australia from the Moreton Bay chestnut *Castanospermum australe*.¹ Biological activities that have been attributed to castanospermine include, but are not limited to, anti-cancer,^{10,11} anti-viral (HIV-1)¹² and anti-diabetic¹³ properties. This biological activity has been shown to be due to the conformational similarity between castanospermine and a glucose residue, as shown in Figure 5, which results in inhibition of glucosidase enzymes.

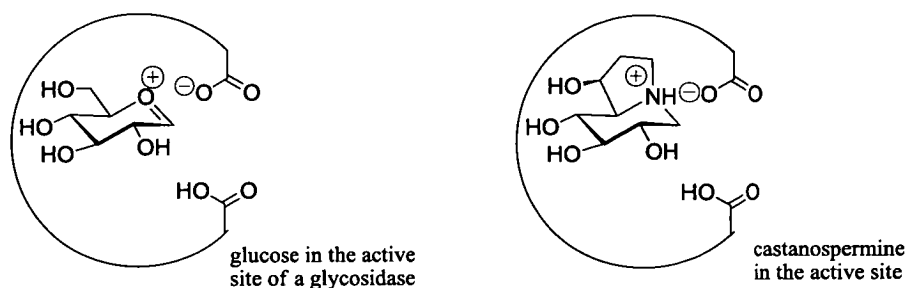


Figure 5: Representation of glucose and castanospermine in the active site of a glucosidase.

(-)-Swainsonine (**8**) is another polyhydroxylated indolizidine that has been shown to have diverse biological activity. (-)-Swainsonine has been found in several species of flora; however, it was first isolated from the fungus *Rhizoctonia leguminicola*.² Like castanospermine, (-)-swainsonine has been shown to inhibit various mannosidases^{14,15} and this has been linked to its various biological properties which led to (-)-swainsonine being the first mannosidase inhibitor to be selected for clinical testing as an anti-cancer therapeutic agent. Initial phase I trial results¹⁶ showed promise, despite the prevalence of hepatotoxicity (chemically-induced liver damage). Phase IB¹⁷ and phase II¹⁸ studies showed a multitude of side effects without sufficient efficacy to justify further clinical studies.

Many other polyhydroxylated indolizidines have been isolated from nature including lentiginosine¹⁹ (**9**), and 2-*epi*-lentiginosine²⁰ (**10**), (Figure 4).

The positioning and stereochemistry of the substituents around the bicyclic system significantly affect the biological activity of the compounds and create opportunities in medicinal chemistry for fine-tuning their activity. These opportunities are reliant on the

development of efficient methods for synthesis of the natural products and analogues. The generation of novel structural analogues by synthesis is essential to develop medicinal activity as there is no other source for these substrates.

1.2 An overview of literature on the synthesis of indolizidine alkaloids

The many approaches to the synthesis of the azabicyclic indolizidine core exploited in natural product syntheses have been reviewed, on a regular basis, by Michael.²¹ A selection of some common retrosyntheses are depicted in Figure 6.

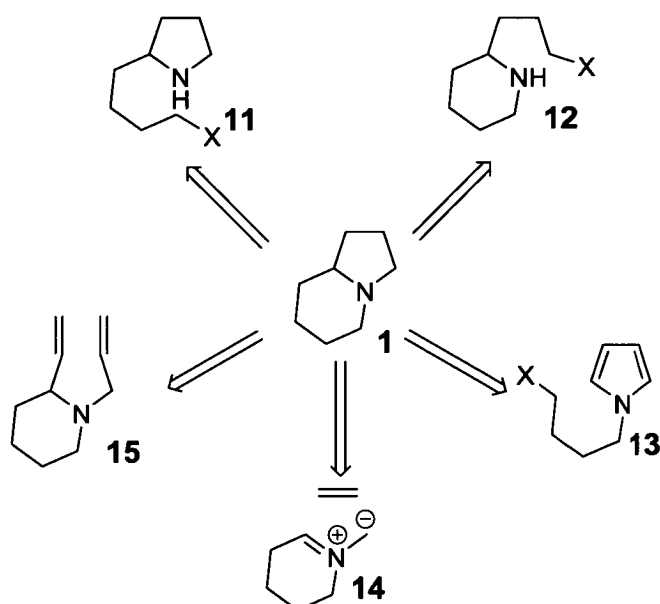
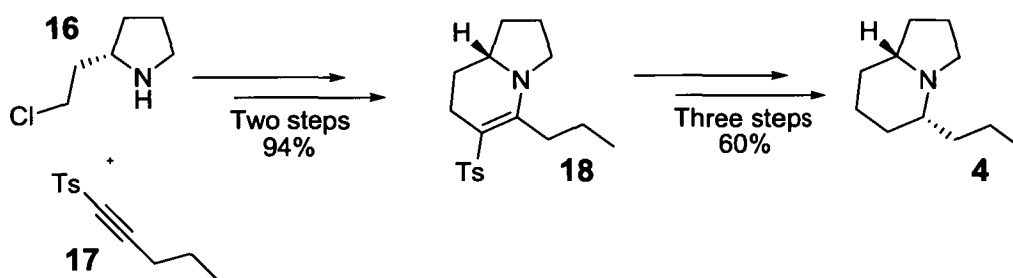


Figure 6: Common retrosyntheses of the azabicyclic indolizidine core.

Common synthetic approaches have utilised the nucleophilicity of the secondary amine of pyrrolidine (**11**) and piperidine (**12**) intermediates to allow cyclisation to yield the azabicycle, through forming either the indolizidine C3-N4 bond or N4-C5 bond.²²⁻²⁴ There have been reports that utilise the nucleophilicity of the 2-position of pyrroles (**13**) to synthesise the azabicycle through cyclisation between C8 and C8a.^{25,26} [3+2] Cycloadditions, e.g. between an azomethine ylide (**14**) and an alkenyl dipolarophile to simultaneously form the C1-C8a and C2-C3 bonds have been reported,^{27,28} as have ring closing metathesis reactions (**15**) using Grubbs RCM catalysts.²⁹

The recent synthesis of (-)-indolizidine 167B (**4**) by Back and Nakajima³⁰ (Scheme 1) is worth highlighting due to its high efficiency. This approach involved the conjugate addition of the nucleophilic amine of the proline derived chloroamine **16** to the alkynyl sulfone **17**, followed by cyclisation to form the unsaturated indolizidine **18**. This synthetic strategy forms the azabicyclic structure through formation of the C6-C7 carbon bond, which is an uncommon approach. Stereoselective hydrogenation of the alkene and reductive cleavage of the sulfone gave the target compound (-)-indolizidine 167B (**4**) in five steps and 56% overall yield from **16**. However, it was necessary to prepare the starting materials, adding several steps to the overall synthesis. The γ -chloroamine **16** was prepared from proline by Arndt-Eistert homologation,³¹ followed by reduction then chlorination, and the sulfone **17** was prepared from 1-pentyne by a two-step selenosulfonation/oxidation/elimination process.³²

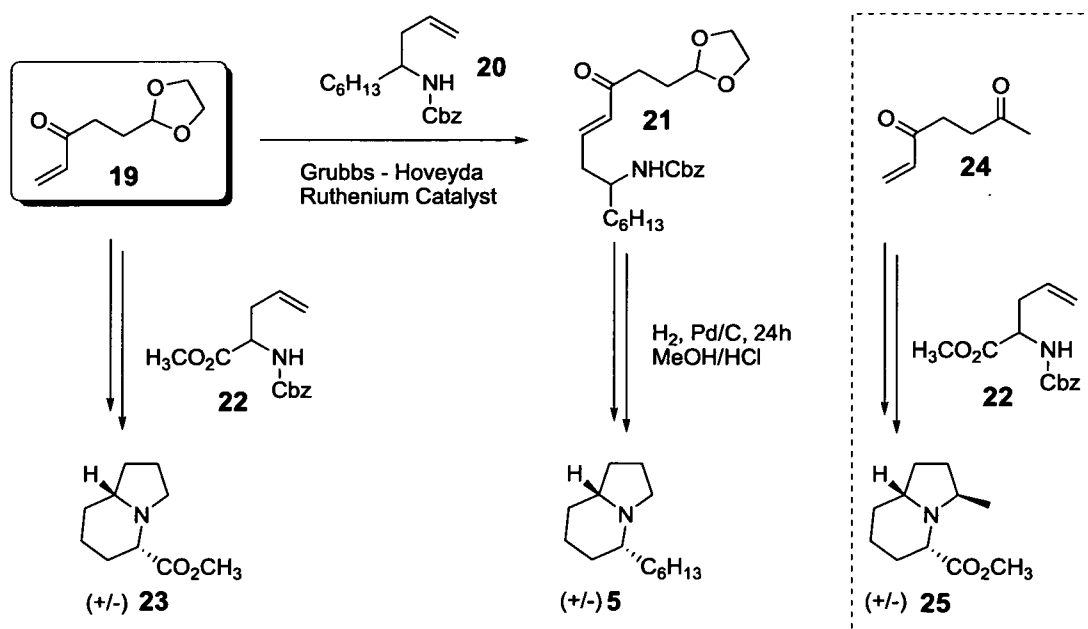


Scheme 1: Nakajima's synthesis of Indolizidine 167B.³⁰

This method provides access to the 5-alkyl indolizidines, however it is not amenable to the efficient synthesis of analogues, for that would require preparation of analogues of **16** and/or **17**. For instance, incorporation of a substituent in the 5-membered ring would require synthesis of a suitably functionalised pyrrolidine intermediate. Incorporation of a different 5-alkyl chain would require a different alkyne starting material as there is limited opportunity to introduce a 5-alkyl substituent at a late stage in the synthesis.

A recent synthesis of 5-alkyl indolizidines reported by Blechert,³³ involves chemistry that could be expanded to the production of a library of 5-alkyl indolizidines from an advanced

intermediate, however, this was not pursued and the approach has only been applied to the synthesis of indolizidine 209D, (Scheme 2).



Scheme 2: Blechert's synthetic approach to indolizidine 209D.³³

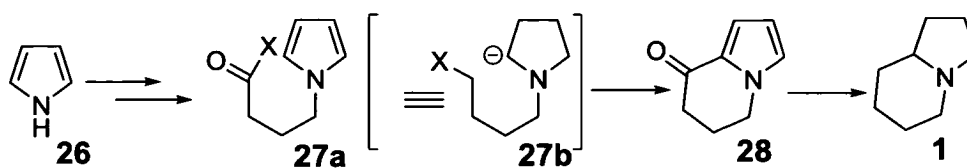
Blechert's method involved a cross metathesis between an α,β -unsaturated ketone **19** and the Cbz-protected amino alkene **20**, promoted in high yield by a Grubbs-Hoveyda ruthenium based catalyst. The metathesis product **21** underwent alkene hydrogenation, hydrogenolysis, acetal deprotection and subsequent two-fold reductive amination to yield the racemic indolizidine 209D (**5**) as a single diastereomer in 77% yield.

Application of a carboxy-substituted amino alkene **22** to the Grubbs-Hoveyda cross metathesis led to the C5-carboxy substituted indolizidine **23**. While not exemplified, the C5 ester could be elaborated to further indolizidine derivatives.²⁵

Blechert applied this method to the synthesis of 3,5-disubstituted indolizidines by varying the α,β -unsaturated ketone. Thus, unsaturated diketone **24** and carboxy-substituted amino alkene **22** yielded the 3,5-disubstituted indolizidine **25** in a stereoselective manner.

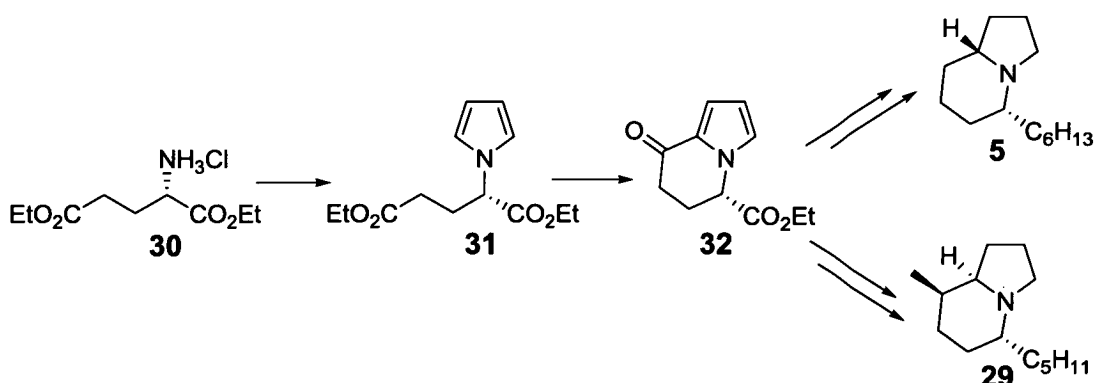
A variation of the azabicyclic indolizidine core retrosynthesis, featuring bond formation between C8-C8a, is to use the electron rich nature of the pyrrole nucleus of *N*-

functionalised pyrrole **27a** as a synthon for a C2-nucleophilic pyrrolidine, such as **27b**. This would result in the pyrroloketone intermediate **28**, which could be exhaustively reduced to yield the fully saturated indolizidine bicycle **1**, (Scheme 3).



Scheme 3: Indolizidine synthesis utilising a pyrrole intermediate.

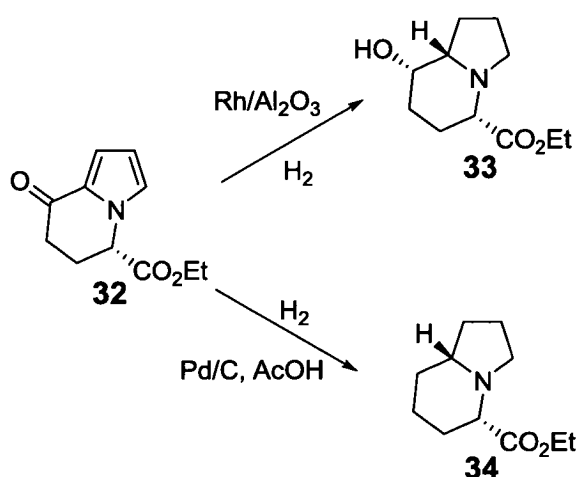
There is precedent for this approach to the preparation of indolizidines. Jefford has reported syntheses of indolizidines 209B (**29**) and 209D (**5**) from an *N*-substituted pyrrole derived from L-glutamic acid.²⁵ This approach involved conversion of diethyl-L-glutamate (**30**) into a γ -pyrrolic ester **31**, which underwent Lewis-acid mediated intramolecular acylation to generate the bicyclic pyrrole intermediate **32**. This advanced intermediate was then manipulated to generate the target natural products, with the 5-ester and 8-keto groups used as handles for further elaboration, (Scheme 4).



Scheme 4: Jefford's synthesis of indolizidines 209B and 209D.²⁵

Jefford²⁵ and Taylor³⁴ independently reported that chemoselectivity for the reduction of α -ketopyrrole bicyclics (**32**) could be achieved through modification of the reduction catalyst and conditions, (Scheme 5). Taylor reported that hydrogenation of **32** over a Pd/C catalyst in the presence of acetic acid resulted in complete hydrogenolysis of the α -keto group and diastereoselective reduction of the pyrrole ring to afford 8-deoxyindolizidine (**34**). In contrast, when the hydrogenation was performed using rhodium on alumina as catalyst, in

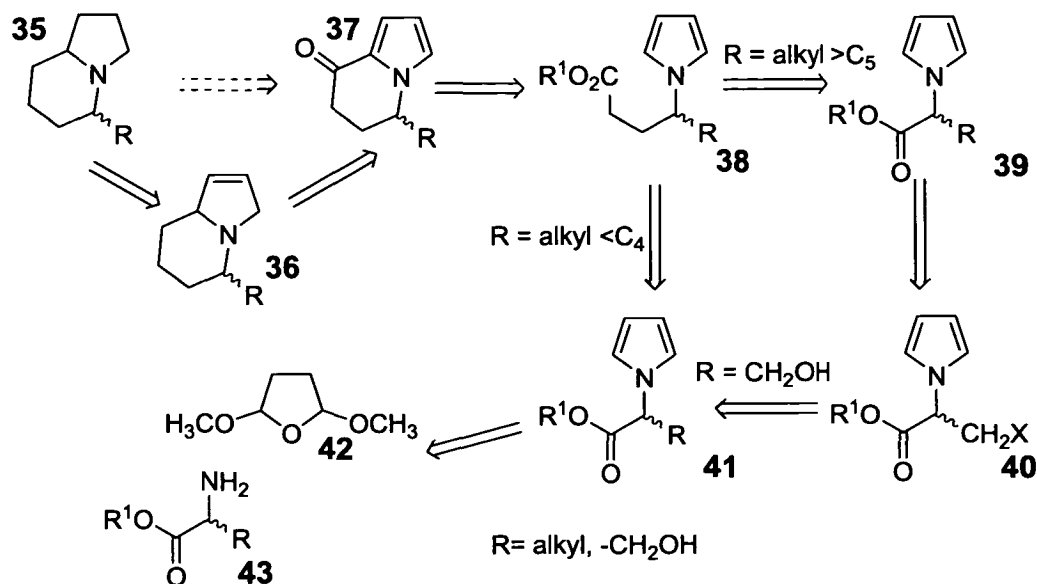
the absence of acid, diastereoselective reduction of the pyrrole ring was again observed along with partial reduction of the ketone giving a single diastereomeric alcohol (**33**). Jefford²⁵ also reported these results for the reduction of **32**, however he also noted that solvent choice has an impact on the relative ratio of hydrogenation to hydrogenolysis of **32**. If hydrogenation of **32** with Pd/C was performed in an ethanol/acetic acid solvent system, higher levels of ethanol led to incomplete hydrogenolysis, with a 99:1 ethanol/acetic acid mixture giving a 39:51 ratio of **34**:**33**. Similarly, when reduction of **32** was performed with Rh/Al₂O₃ in acetic acid, a 16:63 ratio of **34**:**33** was reported.



Scheme 5: Chemoselective reduction of α -ketopyrrole bicyclics.^{25,34}

1.3 Proposed approach to indolizidine synthesis

Given the interest in indolizidine alkaloids as synthetic targets, we decided to focus our efforts on the 5-alkylindolizidines. We chose to approach the 5-alkyl indolizidines using a similar synthetic route to Jefford's synthesis of indolizidine 209D, with a focus on investigating whether α -amino acids could be used as a direct source of the alkyl functionality at C5 of the indolizidine. The retrosynthetic analysis is shown in Scheme 6.



Scheme 6: Retrosynthetic analysis of 5-alkylindolizidines.

The target 5-alkyl indolizidine core **35**, can be obtained through reduction of the corresponding bicyclic α -ketopyrrole intermediate **37**. As mentioned previously, exhaustive hydrogenation/hydrogenolysis has been reported to be a useful method for this transformation.^{25,34} However, that method requires long reaction times and high pressures of hydrogen.^{25,34} Thus, our retrosynthesis involves formation of the 5-alkylindolizidine core **35** by hydrogenation of pyrroline **36** under standard conditions. Pyrroline **36** would be formed by partial reduction of bicyclic pyrrole intermediate **37**. For the partial reduction we wished to investigate whether Knorr and Rabe's method for dissolving metal reduction of pyrroles could be applied to the α -keto pyrroles, such as **37**.³⁵

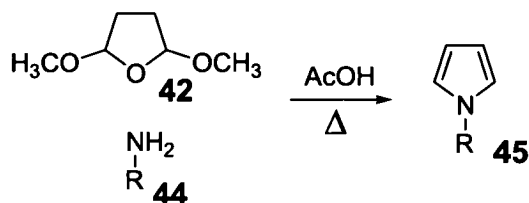
The bicyclic α -keto pyrrole **37**, could be obtained as per Jefford,^{25,36} *via* an intramolecular Lewis-acid mediated acylation of γ -pyrrolic ester **38**. γ -Pyrrolic ester **38** could be produced by two-carbon homologation of α -pyrrolic esters **39** or **41**, by a one-pot DIBAL-H reduction/Wadsworth-Emmons olefination,³⁷⁻⁴⁰ and hydrogenation of the subsequent α,β -unsaturated ester. For C5-alkyl indolizidines with an alkyl chain less than 4 carbon atoms long, the alkyl chain can be introduced by application of the Clauson-Kaas pyrrole synthesis, involving condensation of 2,5-dimethoxytetrahydrofuran **42** and chiral pool amino ester **43**. Whilst enantiopure alkyl amino acids are commonly available and affordable up to the

propyl derivative norvaline, for longer chain derivatives, we propose the α -pyrrolic ester **39**, could be installed by organocuprate reaction with halide **40**. The use of such weakly basic reagents would reduce the possibility of epimerisation and loss of chirality. The halide **40** could be obtained from chiral alcohol **41**, which would come from Clauson-Kaas reaction with serine derivative **43**. At the outset we realised this first step would require studies into identification of very mild reaction conditions, to prevent side-reactions such as epimerisation and elimination, which have been reported in the case of serine methyl ester **43** using the Clauson-Kaas pyrrole synthesis. Installation of the longer chain R-groups at the later stage of the synthesis would make the synthesis more amenable to the production of analogues and allow for the production of a greater range of derivatives than could be obtained using R-groups derived from chiral pool amino acids.

1.4 Pyrrole synthesis

1.4.1 Introduction to the Clauson-Kaas pyrrole synthesis

A classical method for the synthesis of *N*-substituted pyrrole derivatives is the Clauson-Kaas pyrrole synthesis, which involves the condensation reaction of a primary amine **43** with 2,5-dimethoxytetrahydrofuran **42** to yield the corresponding *N*-substituted pyrrole **45**, (Scheme 7).⁴¹



Scheme 7: Generic Clauson-Kaas pyrrole synthetic scheme.

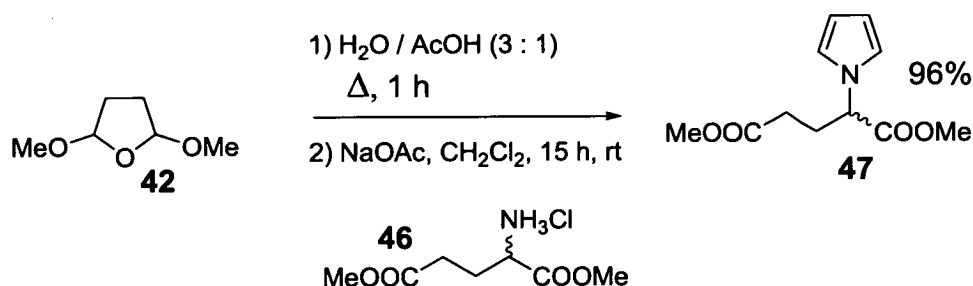
A range of methods have been developed for this condensation,^{42,46} but they typically involve forcing conditions (e.g. refluxing acetic acid), and result in moderate yields due to the reactive nature of the electron-rich pyrrole moiety, which is sensitive to acid and heat. The method developed by Jefford for the Clauson-Kaas pyrrole synthesis and utilised in his reported synthesis of indolizidines 209B and 209D involved a two phase reaction system of dichloroethane / dilute hydrochloric acid or acetate buffer.²⁵ This reduced contact of the acid-sensitive pyrrole products with the acidic medium thought necessary for the reaction to proceed, and resulted in yields of up to 81%.^{25,47} Whilst this was an improvement, these conditions still required heating at 80°C, and in the case of chiral *N*-substituted pyrroles these conditions led to epimerisation, leading to a reduction in the enantiomeric excess (ee) when the reaction was prolonged. The physical appearance of the reactions was reported to be dark, indicative of pyrrole decomposition.

Therefore, for asymmetric synthesis of the desired 5-alkyl indolizidine natural products **35**, we sought a milder method for formation of *N*-substituted pyrroles. In previous work by Gourlay at the University of Tasmania the Clauson-Kaas pyrrole synthesis was separated

into two distinct synthetic operations.⁴⁸ Merz reported that hydrolysis of 2,5-dimethoxytetrahydrofuran to the dialdehyde **48**, (which is present as 2,5-dihydroxyfuran **49** in aqueous solution), required high temperatures and an acid catalyst.⁴⁹ We expected that the condensation of the dialdehyde with the amine (i.e. Paal-Knorr^{50,51} reaction) could be performed under mild conditions. Thus by deconvoluting the Clauson-Kaas synthesis into two distinct steps we had hoped to avoid the exposure of the pyrrole product to the heat and strong acid required for hydrolysis of 2,5-dimethoxytetrahydrofuran.

The hydrolysis of 2,5-dimethoxytetrahydrofuran **42** is typically achieved using mineral acids such as hydrochloric or sulfuric acid,⁴²⁻⁴⁶ however the investigations of Gourlay showed refluxing aqueous acetic acid was suitable for this purpose.⁴⁸

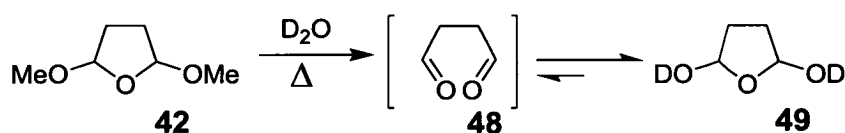
Thus, the Clauson-Kaas reaction was optimised by splitting the reaction into two steps under an atmosphere of N₂, with the hydrolysis step being performed in refluxing dilute acetic acid. The mixture containing the dialdehyde **48** was cooled, buffered with sodium acetate to pH 4.75, and the amine and dichloromethane were added. The condensation proceeded at room temperature, and the two-phase system minimised contact of the pyrrole product with the slightly acidic buffered aqueous layer. For example, when the hydrochloride salt of DL-glutamic acid dimethyl ester **46** was used, the corresponding pyrrole **47** was formed very cleanly and isolated in high yield (96%), (Scheme 8). This yield compares favourably with that reported by Jefford (81%) for the chiral pyrrole **31**.²⁵



Scheme 8: Gourlay's optimisation of the Clauson-Kaas reaction.

1.4.2 Further optimisation of the Clauson-Kaas pyrrole synthesis

Prior to extending the previous Clauson-Kaas pyrrole synthesis optimisation of Gourlay⁴⁸ to the synthesis of chiral pyrrole derivatives from α -amino acids for elaboration towards indolizidines, further investigation of the reaction was undertaken. In order to understand the processes and kinetics of the hydrolysis reaction, we followed it using ^1H NMR spectroscopy, (Scheme 9). Hydrolysis of 2,5-dimethoxytetrahydrofuran **42** in D_2O with acetic acid was monitored by noting the disappearance of the signals due to the starting material methyl ether protons at δ 3.13 and 3.17 ppm, and the formation of signals due to the methine protons of dihydroxytetrahydrofuran **49** between δ 5.36-5.59 ppm. In the presence of one equivalent of acetic acid at 100°C , the reaction was observed to be complete within an hour.



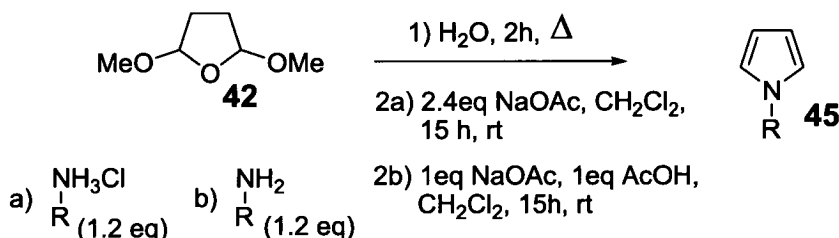
Scheme 9: NMR analysis of the D_2O hydrolysis of 2,5-dimethoxytetrahydrofuran.

This demonstrated that hydrolysis could be performed with mild aqueous acid. One equivalent of sodium acetate was added to the NMR tube to form a buffer of $\approx \text{pH } 5$, and then ammonium chloride was added as a source of ammonia. This led to formation of pyrrole, clearly evident by the appearance of “apparent triplets” at 6.26 and 6.96 ppm due to the two pairs of magnetically non-equivalent protons of the pyrrole ring.

Surprisingly, when the hydrolysis was performed in refluxing D_2O in the absence of any acid, complete D_2O hydrolysis of the acetal was also observed inside two hours, demonstrating that acid catalysts were not necessary for the hydrolysis to occur. To this NMR solution of the 2,5-tetrahydrofuran diol **49** ammonia was added; however, only a trace of pyrrole was observed. Therefore acid catalysis ($\text{pH} \approx 5$) is required for pyrrole formation. The hydrolysis of the 2,5-dimethoxytetrahydrofuran **42** was required for pyrrole formation at room temperature. This was confirmed by a blank test reaction performed by

adding a buffered acid solution of ammonium chloride to a solution of 2,5-dimethoxytetrahydrofuran in D₂O. No evidence for pyrrole formation could be found in the ¹H NMR spectrum.

These results show that the hydrolysis of the 2,5-dimethoxytetrahydrofuran does not require acid; however, the condensation with the amine does require slightly acidic conditions. This led to the investigation of an optimised synthetic method for Clauson-Kaas pyrrole synthesis (Scheme 10). 2,5-Dimethoxytetrahydrofuran **42** was heated to reflux in water for two hours under N₂, then cooled, buffered by addition of an equivalent each of sodium acetate and acetic acid, followed by addition of dichloromethane and the amine. The reaction was stirred for 16h at room temperature (≈18°C), with exclusion from light. In the case of amino ester condensations, where the amine is present as its hydrochloride salt, two equivalents of sodium acetate were added and acetic acid was not required.



Scheme 10: Improved Clauson-Kaas conditions.

These new pyrrole synthesis conditions were tested with a variety of amines, and high yields and ee's were obtained (Table 1), leading to publication of the method in *Tetrahedron Letters*.⁵²

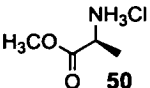
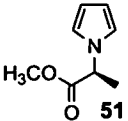
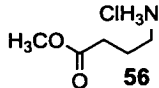
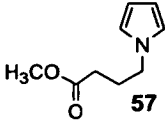
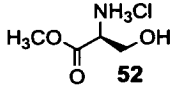
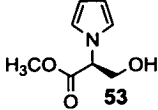
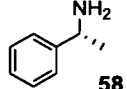
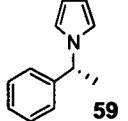
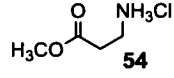
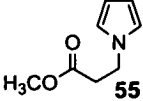
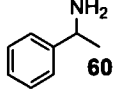
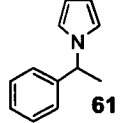
Amine	Product	(%)	ee	Amine	Product	(%)	ee
		93	>99			91	
		89	>99			91	>99
		90				89	

Table 1: Improved Clauson-Kaas pyrrole synthesis.

N-Substituted pyrrole **51** was formed in high yield from L-alanine methyl ester hydrochloride (**50**) and the NMR data was congruent with that reported previously.^{48,53} The enantiomeric excess was determined by comparison of the chiral GC of **51** with that of a racemic sample previously synthesised, (Figure 7).⁴⁸ The result indicated that no epimerisation was observed, even with prolonged reaction times.

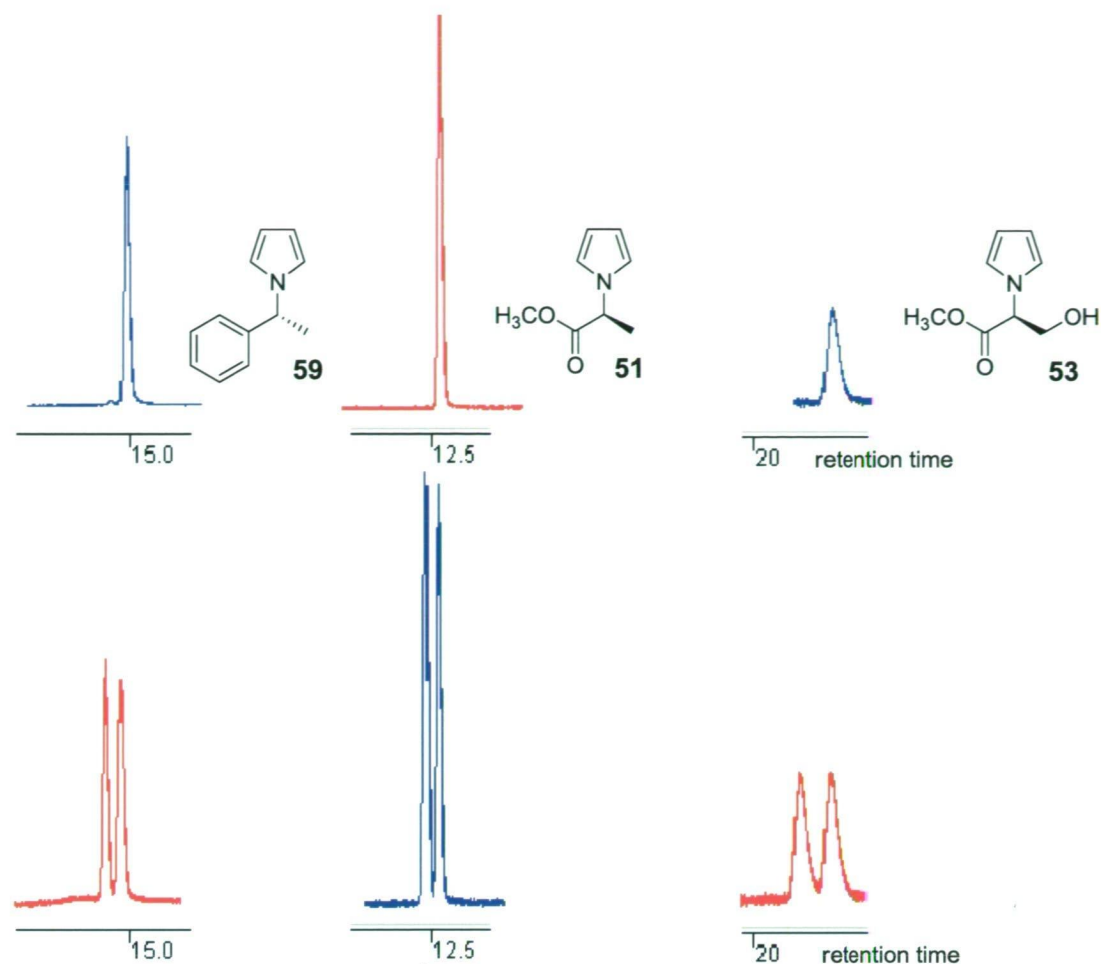


Figure 7: Chiral GC analysis of enantiopure and racemic pyrroles.

Pyrrole **53**, is prone to undergo elimination of water, which was probably the reason for the reported yield of 19% when prepared using an acetic acid/sodium acetate buffer.⁵⁴ Under our conditions **53** was isolated in 89% yield. The diagnostic spectroscopic feature for the synthesis of **53** was the resonance between δ 4.01-4.16 ppm, assigned to the diastereotopic protons of the methylene group. Again, chiral GC showed only one enantiomer.

Similarly, β -pyrrolic ester **55** was identified by comparison to the spectroscopic data published by Domb,⁵⁵ with the pair of triplets ($J = 6.9$ Hz), for the two methylene groups between the pyrrole and ester functionalities a diagnostic feature.

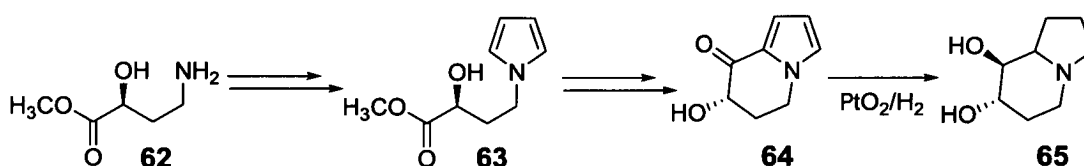
γ -Pyrrolic ester **57** was isolated in high yield and the structure was confirmed through comparison with the literature data,⁵⁶ the key identifier being three methylene resonances and a methyl group in the ^{13}C DEPT spectrum.

The NMR and IR spectroscopic data for pyrroles **59** and **61**, synthesised from *R*- and racemic 1-phenylethylamine respectively, were identical to that reported by Patterson.⁵⁷ The enantiopurity of **59** was determined through chiral GC comparison to **61**, (Figure 7).

These conditions allowed the synthesis of acid and heat-sensitive pyrrole derivatives in excellent yields and enantioselectivities that could not be achieved using current literature methods. This was an excellent result as the reaction yields were not affected by the reaction time. Jefford's conditions only gave high enantioselectivities when the reaction time was minimised, otherwise epimerisation of the stereogenic centre occurred. Thus, his conditions gave higher yields at the expense of enantiopurity, or *vice-versa*.

1.4.3 Clauson-Kaas synthesis of poly-hydroxylated *N*-alkyl pyrrole derivatives

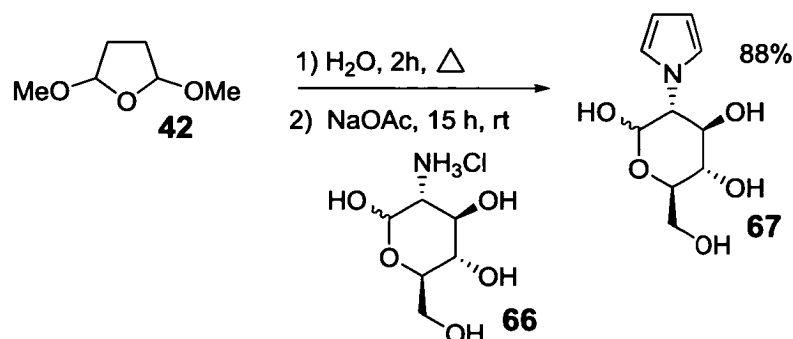
In previous work at the University of Tasmania,⁴⁸ Gourlay synthesised the dihydroxy indolizidine **65**, by Clauson-Kaas synthesis of **63** from the corresponding 4-amino-2-hydroxy butyrate **62**, cyclisation of **63** to give **64**, through a boron tribromide mediated intramolecular acylation, before chemoselective hydrogenation with Adams' catalyst (PtO₂) to yield **65**, (Scheme 11).



Scheme 11: Synthesis of a dihydroxy indolizidine.⁴⁸

Using this method we successfully introduced oxygenation onto the six-membered ring of the indolizidine core. Hydroxylated γ -amino esters are of limited availability, so we decided to investigate amino sugars as a chiral pool source of polyhydroxy alkylamine compounds, and see whether they could be utilised in our modified Clauson-Kaas reaction.

Commercially-available glucosamine **66** was subjected to the improved Clauson-Kaas pyrrole synthesis, (Scheme 12). Due to the polar nature of the product, meaning it would not be soluble in dichloromethane, the reaction was performed only in water.



Scheme 12: Synthesis of a polyhydroxylated *N*-substituted pyrrole derivative.

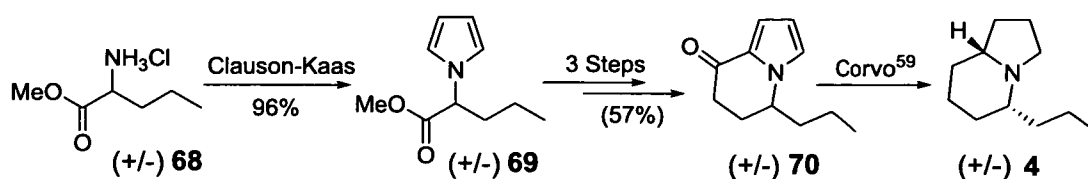
The isolation procedure for pyrrole **67** was also altered. The reaction mixture was concentrated, and the pyrrole purified through silica with methanol/dichloromethane as the eluent (1:4).

The polyhydroxy alkyl pyrrole **67** was isolated in an excellent yield of 88% as a 2:1 mixture of anomers, as confirmed by ^1H NMR spectroscopy, in particular the appearance of the characteristic apparent triplets of the *N*-substituted pyrrole ring at δ 6.21 and 6.88 for the major anomer and δ 6.19 and 6.93 for the minor anomer. Unfortunately, epimerisation of the anomeric centre of D-glucosamine occurred during the pyrrole synthesis, as the commercial sample **66** was present as a 5:1 mixture of anomers. Salmón had previously reported the synthesis of **66**,⁵⁸ however, he obtained it through the Clauson-Kaas reaction of tetra-acylated D-glucosamine and then deprotection, giving a 5% yield over 5 steps. Importantly Salmón reported that all efforts to obtain **67** directly from D-glucosamine using the typical Clauson-Kaas conditions (AcOH, reflux) yielded “an intractable mixture of compounds”.⁵⁸

1.5 Synthesis of aza-bicyclic indolizidine core

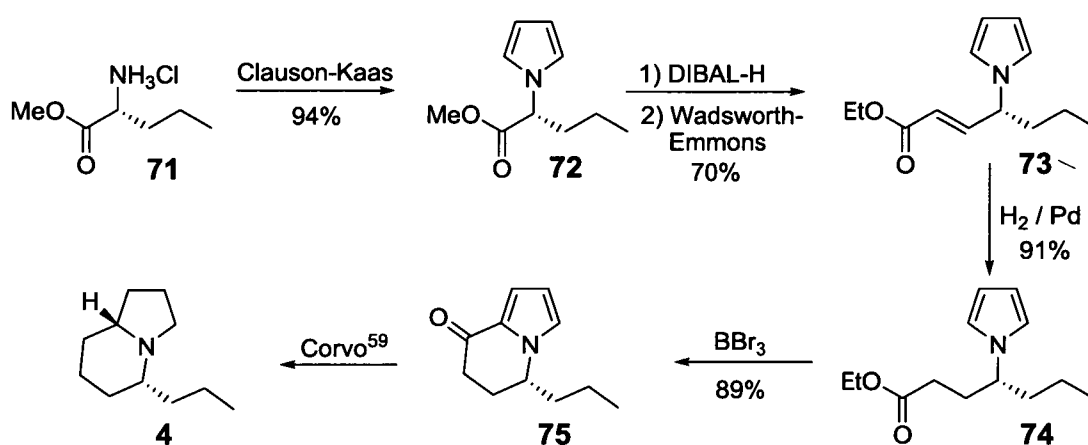
Previous work by Gourlay at the University of Tasmania utilised DL-norvaline in a formal total synthesis of (\pm)-indolizidine 167B,⁴⁸ (Scheme 13). Pyrrole **69** was obtained in excellent yield from DL-norvaline methyl ester hydrochloride **68**, through the originally optimised Clauson-Kaas conditions. Two-carbon homologation and cyclisation gave bicyclic pyrrole

70, which represented a formal synthesis of (\pm)-indolizidine **167B** as Corvo *et al.* converted **70** into indolizidine **167B**.⁵⁹



Scheme 13: Previous racemic formal synthesis of indolizidine **167B**.⁴⁸

Thus, with the further developed Clauson-Kaas conditions, the chemistry was repeated starting with enantiopure D-norvaline methyl ester hydrochloride **71**, allowing for an asymmetric formal synthesis of indolizidine **167B**, (Scheme 14).



Scheme 14: Asymmetric formal synthesis of indolizidine **167B**.

Subjecting D-norvaline methyl ester hydrochloride to the modified Clauson-Kaas method gave pyrrole **72** in 94% yield. The spectroscopic data was identical to that obtained previously for racemic pyrrole **69**.⁴⁸ Chiral GC comparison between pyrrole **72** and a sample of the racemic pyrrole **69** showed that no detectable epimerisation of the stereogenic centre within **72** had occurred.

The two carbon homologation of esters to α,β -unsaturated esters is typically performed⁶⁰ by a three step process, involving reduction of the ester to the alcohol, Swern oxidation to the aldehyde, then olefination under Wadsworth-Emmons conditions.³⁷ However, the two-carbon homologation of **72** to **73** was effected by a one-pot *di*-isobutylaluminium hydride (DIBAL-H) ester reduction followed by Wadsworth-Emmons olefination sequence.³⁸⁻

⁴⁰ Addition of one equivalent of DIBAL-H to the ester **72** in dichloromethane at -78°C resulted in formation of the aldehyde. The anion of triethylphosphonoacetate in THF was added at this temperature, the reaction was then warmed to room temperature, yielding the Wadsworth-Emmons olefination product. This one-pot transformation gave the product in 70% yield, and is a good alternative to the normal 3-step protocol. It has been previously noted that the ratio of solvents is important.⁴⁸ When the ratio of tetrahydrofuran to dichloromethane is above 1:9 then increasing amounts of the *Z*-isomer is observed. Whilst not important in our synthetic sequence, the alkene could be utilised here as a structural tool to introduce functionality into the 6-membered portion of the azabicycle, and thus stereocontrol in the alkene formation could be important. In this case, the spectroscopic data for **73** was identical to the previously prepared racemic material, and the coupling constant for the alkenyl protons ($J = 15.6$ Hz) was consistent with formation of the *E*-isomer.⁴⁸ Hydrogenation of **73** in the presence of catalytic palladium on carbon gave the saturated derivative **74**, and again the spectroscopic data obtained for the product was congruent with that of the previously prepared racemic material. A comparison of the chiral GC of **74** against the previously prepared racemic material showed that no observable epimerisation had occurred during the synthetic sequence.

Intramolecular Friedel-Crafts cyclisation of **74** was promoted by the Lewis acid boron tribromide in dichloromethane (a non-coordinating solvent). The Lewis acid coordinates to the carbonyl group, activating it towards nucleophilic attack by the tethered electron rich pyrrole. The spectroscopic data for **75** was congruent to the racemic derivative **70** prepared previously, and also to that of **75** reported by Corvo.⁵⁹ We noted that in the ¹³C NMR the carbonyl carbon shifted from δ 173 ppm for **74** to δ 187 ppm for **75**, which is consistent with the change from an ester to a ketone. The vinylogous amide character of **75** is indicated by the IR stretching frequency $\nu_{C=O}$ 1660 cm⁻¹.

The production of **75** represents an asymmetric formal synthesis of indolizidine 167B, as Corvo reported hydrogenation of **75** to yield indolizidine 167B.⁵⁹

There are many other chiral indolizidine alkaloids that feature an alkyl functional group in the C-5 position, and in principle the above synthetic approach provides access to these targets utilising α -amino acids as chiral building blocks. Daly has reported the discovery of several indolizidines belonging to different substitution classes that feature an *n*-butyl group in the C5 position.³ These include the 5,8-disubstituted indolizidines 195I (**76**) and 223J (**77**), as well as the 3,5-disubstituted indolizidine 253T (**78**) (Figure 8).

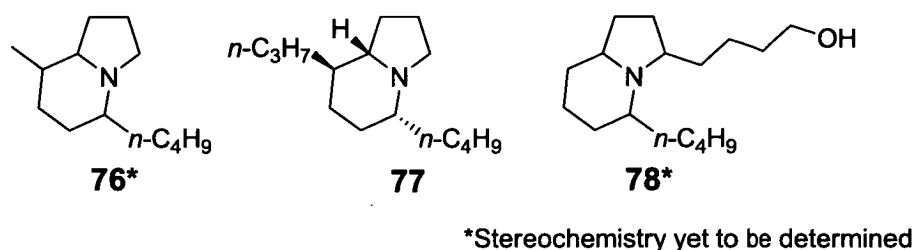
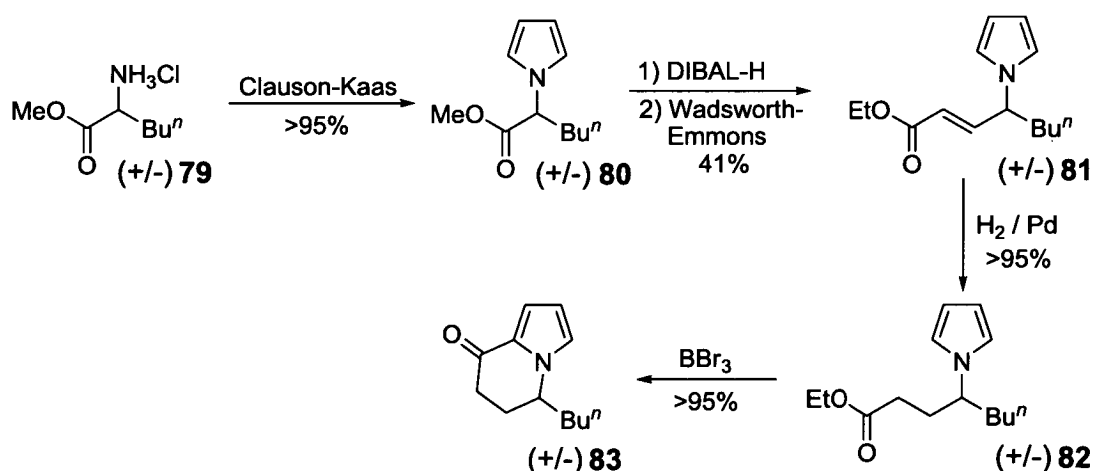


Figure 8: C5-Butyl substituted indolizidines.

Thus, to introduce a butyl group to the indolizidine C5 position, norleucine is required. The chirality of the natural product targeted determines which enantiomer of norleucine would be required. Due to the prohibitive cost of enantiopure material, racemic amino acid was utilised to demonstrate a racemic synthesis of a C5-butyl indolizidine, (Scheme 15).



Scheme 15: C5-Butyl azabicyclic core construction.

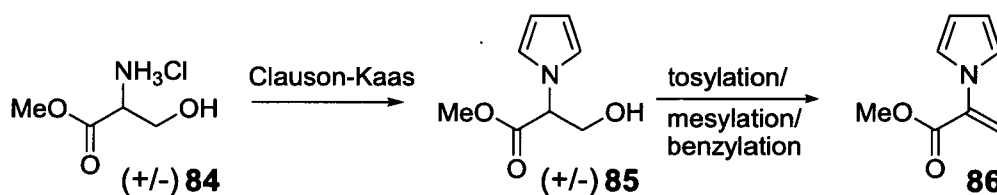
Following the method as for the propyl derivative, pyrrole formation followed by two-carbon homologation and intramolecular Friedel-Crafts acylation led to the bicyclic keto-pyrrole **83** in 55% yield over 4 steps from the methyl ester hydrochloride of (\pm)-norleucine

79. Indolizidine **83** was not elaborated to its fully saturated analogue as this was beyond the scope of the project, but this transformation could be chemoselectively performed as mentioned in the introduction.

As indicated by the cost of D-norleucine,^b the cost or lack of availability of enantiopure higher homologues of the amino acids meant that an alternative general method for the synthesis of 5-alkyl indolizidines from a chiral advanced intermediate was desirable.

One α -amino acid possessing a functional group that could allow chain homologation is serine. Conversion of the alcohol of serine derivatives to an alkyl halide or sulfonate would allow chain extension through cuprate chemistry, such that the choice of cuprate reagent would allow selective synthesis of different indolizidines.

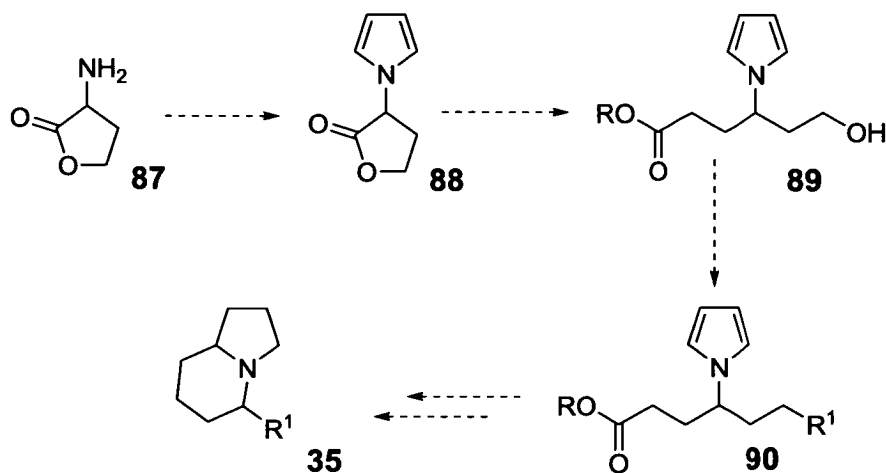
Initial work at the University of Tasmania had shown that activation of the alcohol of the serine derived pyrrole **85** by attempting conversion to the tosylate, mesylate or benzyl ether resulted in elimination processes and formation of **86**, (Scheme 16).⁴⁰ Whilst this derivative could undergo cuprate conjugate addition for the introduction of longer alkyl chains, the stereochemistry derived from the starting material was lost, and this defeats the purpose of utilising a chiral pool starting material.



Scheme 16: Previous attempts to functionalise serine derived pyrrole.⁴⁰

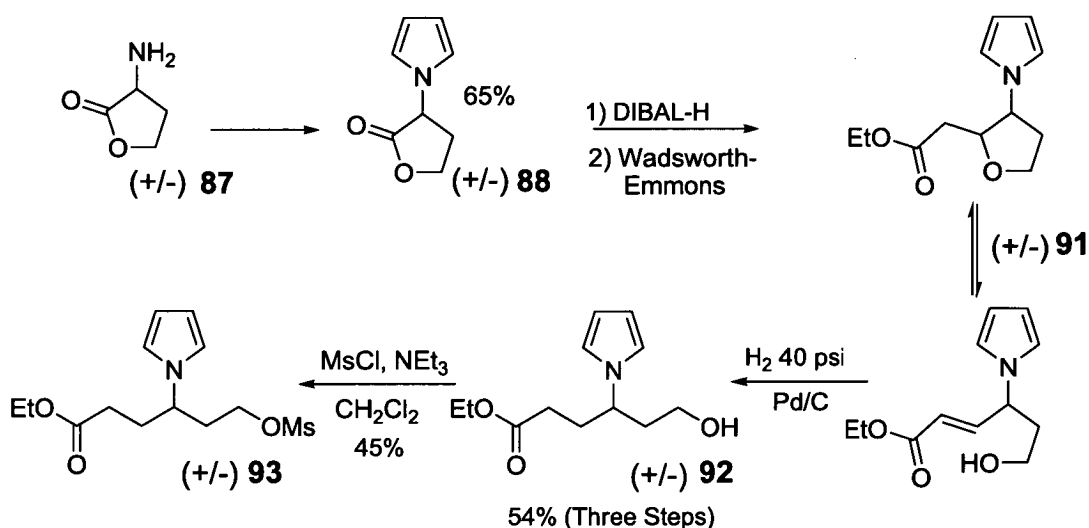
It was then hypothesised that homo-serine **87** would be a suitable starting material. Pyrrole (**88**) formation, followed by two carbon homologation would lead to a useful advanced alcohol intermediate (**89**), which could be activated and reacted with organocuprates to introduce a range of R-groups (**90**), then converted to the indolizidines (**35**), (Scheme 17).

^b D-norleucine costs \$50 per 100mg from Sigma Aldrich chemical company (5-8-2009).



Scheme 17: Proposed use of homoserine for C5-alkyl substituted indolizidine synthesis.

As proof of principle experiments, racemic homoserine **87** was converted into an advanced synthetic intermediate **93**, (Scheme 18).



Scheme 18: Development of an advanced synthetic intermediate for 5-alkylindolizidines.

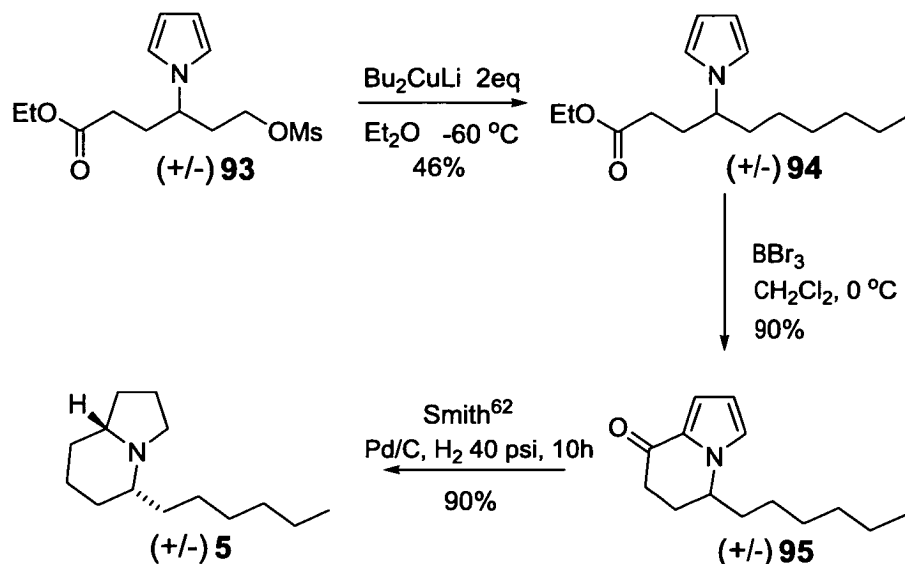
The starting material, homoserine, was prepared from methionine according to the literature procedure.⁶¹ Condensation of homoserine (**87**) with dimethoxytetrahydrofuran according to our modified Clauson-Kaas method, gave the pyrrole **88**, in 65% yield.^c Formation of the pyrrole was indicated in the ¹H NMR spectrum by the appearance of the usual apparent triplets at 6.24 and 6.73 ppm due to the pyrrole protons. The lactone was

^c The low yield is thought to be due to the use of unpurified homoserine in the Clauson-Kaas reaction.

shown to be still present by IR spectroscopy, as the sample displayed a carbonyl stretch at 1781 cm^{-1} , characteristic of a γ -lactone.

Performing the two-carbon homologation on pyrrolic lactone **88** gave the crude α,β -unsaturated ester **91**, as an equilibrium mixture of tautomeric alkenyl alcohol and cyclic ether forms. This mixture was not purified, but was hydrogenated to give alcohol **92**, which was purified by chromatography and isolated in 54% yield over the three steps from lactone **88**. The ^1H NMR spectrum of pyrrole **92** was consistent with the expected structure, as was the ^{13}C NMR spectrum featuring 10 signals, including 7 aliphatic carbon resonances. The mass spectrum of the product showed a molecular ion of m/z 225, consistent with the structure **92**. The reaction of **92** with mesyl chloride gave the mesylate **93** in 45% yield (not optimised, as it was only performed once). The ^1H NMR spectrum of the mesylate was similar to the starting alcohol, but did not contain the broad singlet due to the alcohol proton and did contain a singlet at δ 2.89 ppm assigned to the mesylate methyl group. Thus, an important intermediate had been formed towards the establishment of an advanced compound for the synthesis of 5-alkyl indolizidines.

Treating mesylate **93** with the cuprate from *n*-butyl lithium and copper iodide gave hexyl-substituted compound **94** in an unoptimised yield of 46%, (Scheme 19).⁶² The key spectroscopic evidence for formation of **94** was the addition of four signals in the aliphatic region of the ^{13}C NMR spectrum, and the absence of signals due to the mesylate methyl group at δ 37 ppm in the ^{13}C NMR spectrum and δ 2.89 ppm in the ^1H NMR spectrum.



Scheme 19: Formal synthesis of 209D from advanced intermediate.

Cyclisation of the ethyl ester **94** promoted by boron tribromide gave the indolizidine **95** isolated in 90% yield. The spectroscopic data for **95** was identical to that of a sample of **95** prepared previously through a lactone ring opening and cyclisation route, as an intermediate in a total synthesis of (\pm)-indolizidine 209D.⁶²

Hence, this represents a total formal synthesis of (\pm)-indolizidine 209D and provides proof of concept for the use of homo-serine to generate higher homologues of the C-5 alkyl indolizidines.

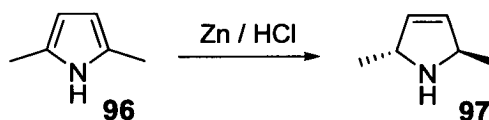
1.6 Indolizidine *via* Knorr-Rabe zinc reduction of α -ketopyrroles

1.6.1 Introduction to the Knorr-Rabe reduction reaction

Whilst catalytic hydrogenations of α -ketopyrroles have been reported to give their unsaturated derivatives with high diastereoselectivity, these reactions involve high pressures of up to 55 psi, and long reaction times, (often days), and sometimes fail to go to completion.^{63,34,59} These problems have been experienced previously within the organic research group at the University of Tasmania, particularly during studies on hydrogenation of **95** to yield indolizidine 209D, (Scheme 19).⁶²

Thus, other methods for reduction of the pyrrole moiety were investigated. There are few reports of dearomatisation in the literature for pyrrole derivatives, with the Birch reaction being utilised in only a handful of instances.⁶⁴ The Birch reaction is a method for the dearomatisation of aromatic derivatives and has been used in natural product syntheses. However, partial reduction of pyrrole derivatives *via* a Birch reduction is difficult as the first step of the reduction mechanism is addition of an electron to the ring which is largely disfavoured due to the high electron density of the pyrrole moiety. This is not to say it cannot be accomplished, as Donohoe has reported that the partial reduction of pyrroles is possible, only when at least two electron withdrawing groups are present.⁶⁴⁻⁶⁶ This shows that electron deficient pyrroles can accept an electron and undergo subsequent reduction. Donohoe recently exploited this reaction for a synthesis of (\pm)-*epi*-australine.⁶⁷ The requirement for these electron withdrawing groups reduces the versatility of this reaction, and hence we looked for an alternative method, more suitable for reduction of electron-rich pyrroles.

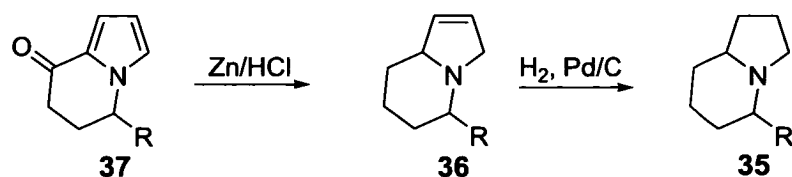
Another method for the reduction of electron-rich pyrroles, which has only been utilised a few times according to the literature is the action of zinc in an acidic media, first reported by Knorr and Rabe in the early 1900's.³⁵ As shown later by McElvain,⁶⁸ through the reduction of 2,5-dimethylpyrrole **96**, the Knorr-Rabe reduction proceeds diastereoselectively yielding the *trans* substituted 3-pyrroline, **97** (Scheme 20).



Scheme 20: Knorr-Rabe partial reduction of 2,5-dimethylpyrrole.³⁵

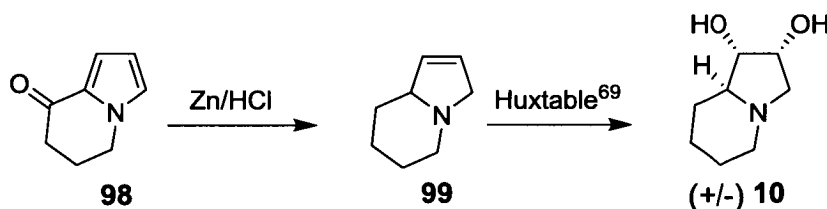
This dissolving metal reduction of the electron-rich pyrrole moiety is potentially a more versatile reaction, as it does not require activation of the pyrrole by electron-withdrawing groups.

Thus, it was proposed the slow and problematic catalytic hydrogenation of the α -ketopyrroles could be replaced by the Knorr-Rabe reduction, followed by hydrogenation of the alkene of the 3-pyrroline formed, (Scheme 21).



Scheme 21: Proposed route to fully saturated indolizidine core.

In previous work at the University of Tasmania, Gourlay showed that this approach was possible.⁴⁸ Starting from an unsubstituted bicyclic indolizidine intermediate **98**, partial reduction under modified Knorr-Rabe conditions gave pyrroline **99**. This reduction occurred quickly (10 mins) and gave the volatile alkene in high yield. The formation of **99** represented a formal total synthesis of (\pm)-1-*epi*-lentiginosine **10**, as the group of Huxtable has previously formed pyrroline **99** as an intermediate in the synthesis of **10**, (Scheme 22).⁶⁹



Scheme 22: Formal synthesis of lentiginosine.⁴⁸

Initial investigations by the group at the University of Tasmania found that reduction of **98** required more forcing conditions than those reported by Knorr and Rabe, and later by Andrews and McElvain.^{39,35,68} The earlier method involved treatment of the pyrrole substrate at low temperature ($<10^\circ\text{C}$) with powdered zinc and 5M hydrochloric acid. The low temperatures were required to reduce side reactions involving over-reduction to give pyrrolidine side products. However, no reaction of α -ketopyrrole **98** was observed using the method of Andrews and McElvain. Conversely, it was shown that when the reaction temperature was increased by adding the zinc and concentrated hydrochloric acid to a

solution of α -ketopyrrole in refluxing methanol, rapid consumption of the starting material and formation of the alkene was observed with minimal over-reduction to the pyrrolidine observed.^{39,48} This was the first example of successful reduction of an α -ketopyrrole using Knorr-Rabe type conditions. The result of the reaction, reduction of both ketone and pyrrole, is similar to that of Birch and Clemmensen reductions.⁷⁰⁻⁷⁶

Hence the pyrroline could be hydrogenated to the pyrrolidine and even though this would be a two-step process, it should have the advantage of being more reliable than the catalytic hydrogenation methods previously reported.

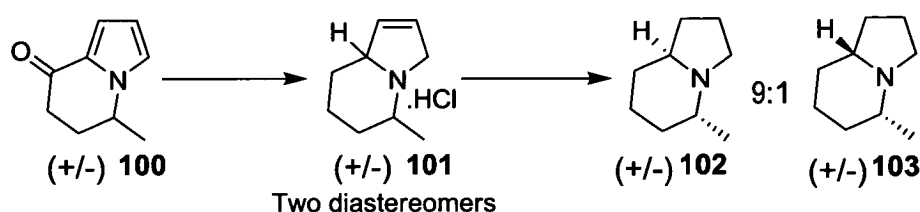
1.6.2: The stereoselectivity of the Knorr-Rabe reduction

In order to determine the stereoselectivity of the reduction of bicyclic keto pyrrole derivatives, the 5-methyl derivative **100** was used as a model system. The Knorr-Rabe reduction of ketopyrrole **98** afforded a racemic pyrroline **99**. With the racemic 5-methyl substituted pyrrole **100**, there is a possibility for formation of two diastereomers, thus **100** seems useful as a model system for probing the stereoselectivity of the Knorr-Rabe reduction.

Model system **100** was prepared from DL-alanine through the Clauson-Kaas, chain homologation and cyclisation route discussed earlier for the synthesis of **75**.⁴⁸

(\pm)-5-Methyl-6,7-dihydroindolizin-8(5H)-one **100** was heated to reflux in methanol, then removed from the heat source. Powdered zinc and hydrochloric acid were added alternately in small portions at a rate to maintain reflux of the solvent. The mixture was made alkaline with concentrated ammonia to solubilise the zinc salts, and extraction with dichloromethane yielded the indolizidine, however due to the volatility of the product the material could easily be lost during rotary evaporation. To avoid such loss, a drop of concentrated hydrochloric acid was added to the CH₂Cl₂ extracts before rotary evaporation such that pyrroline **101** was isolated as its hydrochloride salt, (Scheme 23).

The ^{13}C NMR spectrum of **101** was indicative of the change from a pyrrole to a 3-pyrroline with a reduction in the number of sp^2 hybridised carbons from five to two, including the absence of a carbonyl resonance. Similarly, for the ^1H NMR spectrum of **101**, the characteristic pyrrole proton resonances of **100** were absent and a multiplet of two overlapped protons at δ 5.8 ppm was apparent, representing the alkenyl protons. Although the stereochemistry of the major isomer was not determined, the ^1H NMR spectrum of **101** indicated a major and minor diastereomer in an approximately 9:1 ratio, through the integration of the 5-methyl doublets at δ 0.99 and 1.42 ppm ($J = 6.3$ Hz).



Scheme 23: Knorr-Rabe reduction approach to 5-methyl indolizidine.

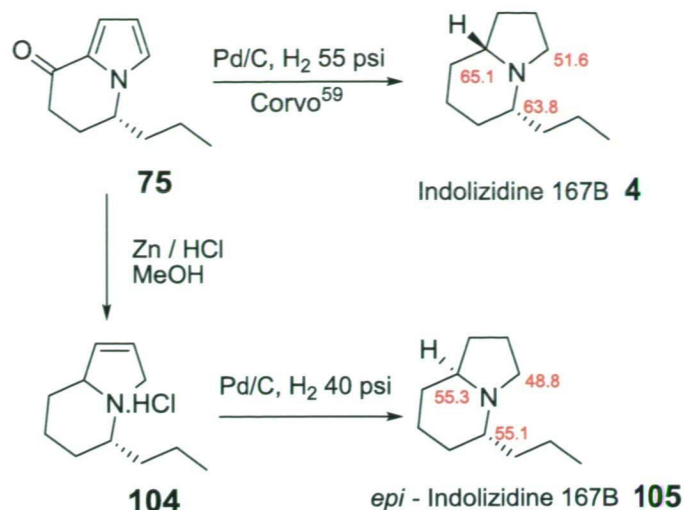
Catalytic hydrogenation of alkenes **101** was complete in 2h, as evidenced by the alkenyl resonances of **101** no longer being present at δ 5.8 ppm, (Scheme 23).³⁹ Analysis of the ^{13}C NMR of the product yielded an interesting result. The reaction maintained the 9:1 mixture of diastereomers, with the minor diastereomer **103** being that which is formed by catalytic hydrogenation of **100**. Therefore the two-step process of partial reduction and hydrogenation had led to a quantitative yield of crude indolizidines, however the major product was the unexpected diastereomer **102**.

The difference between the diastereomers is clearly shown in the ^{13}C NMR spectrum, where the chemical shifts of the three carbons adjacent to the nitrogen in the major diastereomer are at 54.9, 50.2 and 49.1 ppm, and the minor isomer at 64.8, 58.2 and 51.7 ppm. Previous diastereoselective synthesis of both diastereomers by Polniaszek found resonances of 54.5, 50.0, and 49.2 for the *trans* isomer, and 64.8, 58.9 and 51.8 ppm for the *cis* isomer.⁷⁷ (*Trans* isomer refers to the two hydrogens at C5 and C8a being on the opposite face of the bicyclic system, whereas the *cis* isomer refers to the protons on the

same face.) Therefore the major isomer formed by the two-step reduction process was not the isomer formed through catalytic hydrogenation. Jefford,²⁵ Taylor³⁴ and Corvo⁵⁹ have shown previously that the C5 substituent of bicyclic pyrroles forces hydrogen to approach from the least hindered face, therefore leading to the *cis* isomer. It was hypothesised that the stereochemistry of the zinc reduction is a product of the coordination of zinc to the less-hindered face of the nitrogen of pyrrole **100**, therefore causing protonation to occur on the same side as the C5-substituent, resulting in the *trans* stereochemistry.

Thus, while unexpected, this result now allows the controlled synthesis of both diastereomers of an indolizidine from the one common intermediate by choice of the reduction conditions.

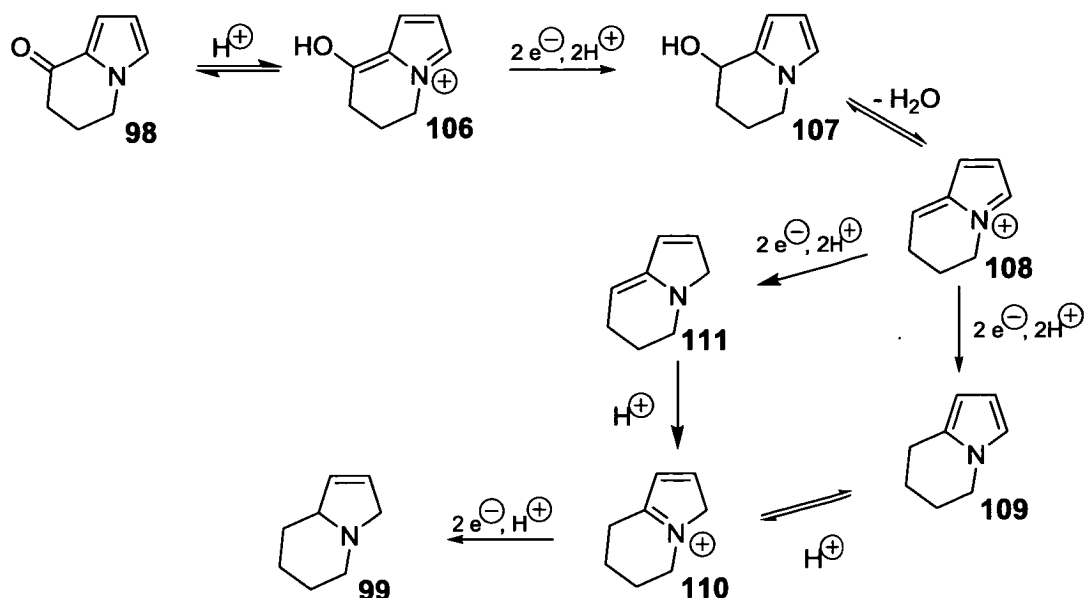
Next investigated was the propyl-substituted bicyclic ketopyrrole **75**, (Scheme 24). Again, when the Knorr-Rabe reduction/hydrogenation sequence was performed on this derivative, two diastereomers were formed in an approximately 9:1 ratio, with the ¹³C NMR spectrum major diastereomer resonances at 55.33, 55.30 and 48.7 ppm and the minor diastereomer resonances at 65.0, 63.7 and 51.5 ppm. As with the C5-methyl substituted case, both the *trans* and *cis* isomers were reported by Polsniaszek, with his reported resonances for the *trans* isomer; 55.3, 55.1 and 48.8 ppm and for the *cis* isomer, (-)-indolizidine **167B**; 65.1, 63.8, 51.6 ppm.⁷⁷ The *cis*-isomer resonances were consistent with those reported by Corvo,⁵⁹ obtained by catalytic hydrogenation of the same intermediate **75**. Therefore, as with the methyl derivative, the *trans* isomer (*epi*-indolizidine **167B**) was the major product.



Scheme 24: Knorr-Rabe reduction approach to *epi*-indolizidine 167B with ^{13}C NMR resonances for C3, C5 and C8a.

Thus the Knorr-Rabe/hydrogenation tandem reduction sequence had allowed the synthesis of *epi*-indolizidine 167B from **75**.

We propose the mechanism of the zinc reduction is as follows, (Scheme 25). There are several possible mechanisms for this transformation, however, we propose that the first step involves protonation of the carbonyl group to give a conjugated iminium ion **106**. This species would undergo a two-electron reduction process, with associated protonation to give the α -hydroxy pyrrole **107**. Acid-promoted dehydration of **107** would afford a second iminium ion **108**, which could undergo further reduction and protonation to give pyrrole **109**. The pyrrole could then be protonated at C3 to give a third iminium ion **110** and reduction would then give rise to the product **99**, which explains the position of the alkene.

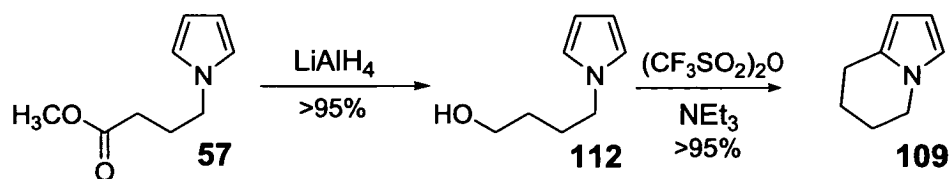


Scheme 25: Proposed mechanism of the Knorr-Rabe reduction of α -ketopyrrole bicyclics.

Our reaction conditions are much harsher than those previously reported, and yet we do not see pyrrolidine products, suggesting that an alternative pathway may be in operation. One possibility is that the intermediate **108** could undergo reduction to give **111** directly without the formation of the pyrrole **109** as an intermediate.

To test these hypotheses we reduced the ketone **98** with NaBH_4 to give the unstable α -hydroxy pyrrole **107**, which was then immediately subjected to the reduction conditions. The 3-pyrroline **99** was isolated cleanly as the sole product of the reduction, lending support to the suggestion that **107** is an intermediate in the reaction.

In order to further test the mechanistic hypothesis, we prepared the pyrrole intermediate **109**. This was synthesised utilising an alternative cyclisation method to yield the aza-bicyclic core, (Scheme 26). γ -Pyrrolic ester **57** was reduced with lithium aluminium hydride to quantitatively give the alcohol **112**. The alcohol **112** was identified through the loss of the methyl ester resonances of the ^1H NMR spectrum of **57**. A new methylene group was observed in the ^{13}C NMR spectrum of **112**, that replaced the carbonyl resonance. Additionally no methyl resonance was observed. Cyclisation of **112** with triflic anhydride and triethylamine following the method of Gmeiner^{78,42} gave **109**, which gave spectral data consistent with that reported previously by Albonico.⁷⁹



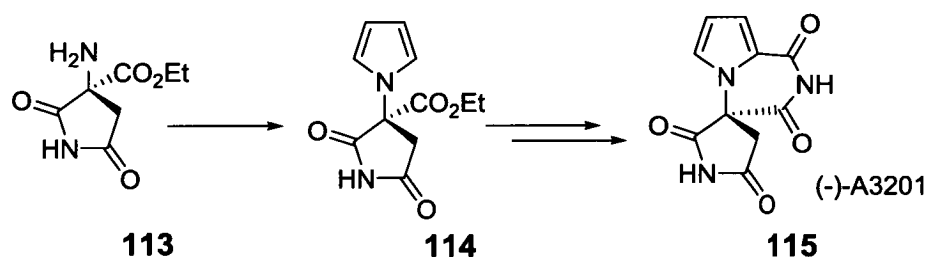
Scheme 26: Synthesis of 8-deoxyindolizidine **109**.

When pyrrole **109** was allowed to react under the normal reduction conditions, pyrroline **99** was formed but the ^1H NMR spectrum showed that some starting material remained. The fact that the pyrrole **109** was not observed in the reduction of the α -ketopyrrole **98** lends support to the suggestion of the alternative pathway in which iminium **108** undergoes reduction and protonation to yield the 3,5,6,7-tetrahydroindolizine **111** directly. However, at the present time the intermediacy of **109** cannot be completely ruled out for the reduction of ketone **98** and alcohol **107**.

1.7 Conclusion

Thus, shown here is an efficient and variable route to synthesise 5-alkyl indolizidines. Optimisation of the Clauson-Kaas pyrrole synthesis has allowed this route to be successful through elimination of the previously reported problems of low yields and epimerisation.

These improved Clauson-Kaas conditions have been used by a Japanese group⁸⁰ in their approach towards an asymmetric synthesis of compound AS-3201 (**115**), currently under development for the treatment of diabetes complications, (Scheme 27).



Scheme 27: Utilisation of our modified Clauson-Kaas synthesis to make (-)-A3201.

Further investigation into the polyhydroxylated pyrrolic-sugars formed by condensation of the amino-sugars may possibly allow elaboration to both known and novel polyhydroxylated indolizidines.

Further 5-alkyl indolizidine derivatives could be targeted through the use of alternative cuprate reagents by changing the alkyl source from *n*-butyl lithium. Investigation into the use of chiral homo-serine could also determine the potential to use this synthetic method for the stereoselective synthesis of indolizidine alkaloids.

The development of the Knorr-Rabe reduction as an alternative pathway to reduce α -ketopyrrole indolizidines to their fully saturated derivatives has allowed the synthesis of the alternative diastereomers to that obtained by the catalytic hydrogenation method, and could play a role in further natural product synthesis due to the diastereoselective outcome.

Chapter 2: Synthesis of pyrrolidine and indolizidine alkaloids using 1,3-dipolar cycloaddition reactions of azomethine ylides

2.1 Pyrrolidine alkaloids

Pyrrolidines are a fundamental class of heterocyclic compounds that contain a fully-saturated 5-membered ring containing one nitrogen atom. There are many examples of naturally-occurring pyrrolidine alkaloids, and they vary greatly in their substitution pattern around the ring. Biological studies on many of the alkaloids have revealed interesting activities, and hence they are challenging and important targets for total synthesis.

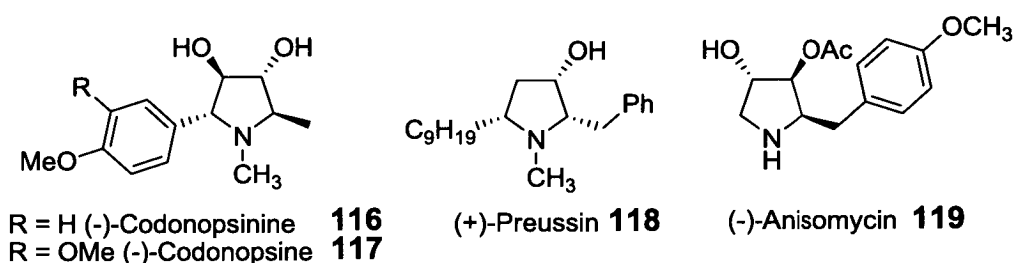


Figure 9: Hydroxylated pyrrolidine alkaloids

(-)-Codonopsinine **116** and (-)-codonopsine **117** (Figure 9) were first isolated from *Codonopsis clematidea*, a plant native to central Asia, in 1969 by the Soviet group of Matkhalikova in what is now Uzbekistan.^{81,82} These alkaloids were the first examples of 1,2,3,4,5-pentasubstituted pyrrolidines found as natural products.

Codonopsinine has been shown to have diverse biological activity, most notably antibiotic and hypotensive activity, without affecting the central nervous system.⁸³ Initial structural characterisation performed by Matkhalikova's group⁸⁴⁻⁸⁶ led to the assignment of the naturally-occurring levorotatory enantiomer (-)-codonopsinine the structure of 2*R*, 3*S*, 4*S*, 5*S*; however after the total synthesis of 4 diastereomers by Kibayashi the structure was revised to 2*R*, 3*R*, 4*R*, 5*R*.⁸⁷⁻⁸⁹

Another similar hydroxylated pyrrolidine (+)-preussin **118** was first isolated from the fermentation broths of the fungus *Aspergillus ostraceus* in 1988 by a group of researchers

from Merck.⁹⁰ They were able to identify the structure and designated it L657,398, however they were unable to determine the relative stereochemistry by NMR spectroscopy. Initial biological testing by the Merck group reported it to have anti-fungal activity. Seven months later a group from the Squibb Institute reported the isolation of the same compound from the fermentations broths of *Preussia* sp.⁹¹ The Squibb group were able to determine the absolute stereochemistry by NOE experiments and gave the name preussin to this compound. Since then, preussin has been the subject of various biological testing and found to have growth-inhibitory and cytotoxic effects on human cancer cells, making it a good lead structure for the development of anti-tumour agents.⁹²

(-)-Anisomycin **119** was first reported by researchers from Pfizer in 1954, who isolated it from *Streptomyces griseolus*,⁹³ and found it to exhibit potent activity *in vitro* against pathogenic protozoa *Trichomonas vaginalis* and *Endamoeba histolytica*.⁹³ The relative stereochemistry of (-)-anisomycin was determined in 1967 through X-ray crystallographic studies,⁹⁴ and the above configuration was later determined by Wong,⁹⁵⁻⁹⁷ when he completed the first asymmetric total synthesis. (-)-Anisomycin has been the subject of extensive biological activity studies, exhibiting anti-tumour activity,⁹⁸ and has been used in molecular biology studies due to its protein synthesis inhibition. (-)-Anisomycin and (+)-preussin were also shown to exhibit anti-viral activity through their ability to block viral propagation in RNA based viruses, and hence represent good lead structures for new anti-viral agents.⁹⁹

Not all biologically-active pyrrolidine alkaloids bear hydroxyl substituents and an example of these are the kanoids.¹⁰⁰ These are a group of pyrrolidine dicarboxylic acids that have been long used as insecticides and anthelmintics,¹⁰⁰ but their principal use now is as conformationally-restricted analogues of the neurotransmitter glutamic acid, and are hence valuable tools in neurofunctional studies.¹⁰¹

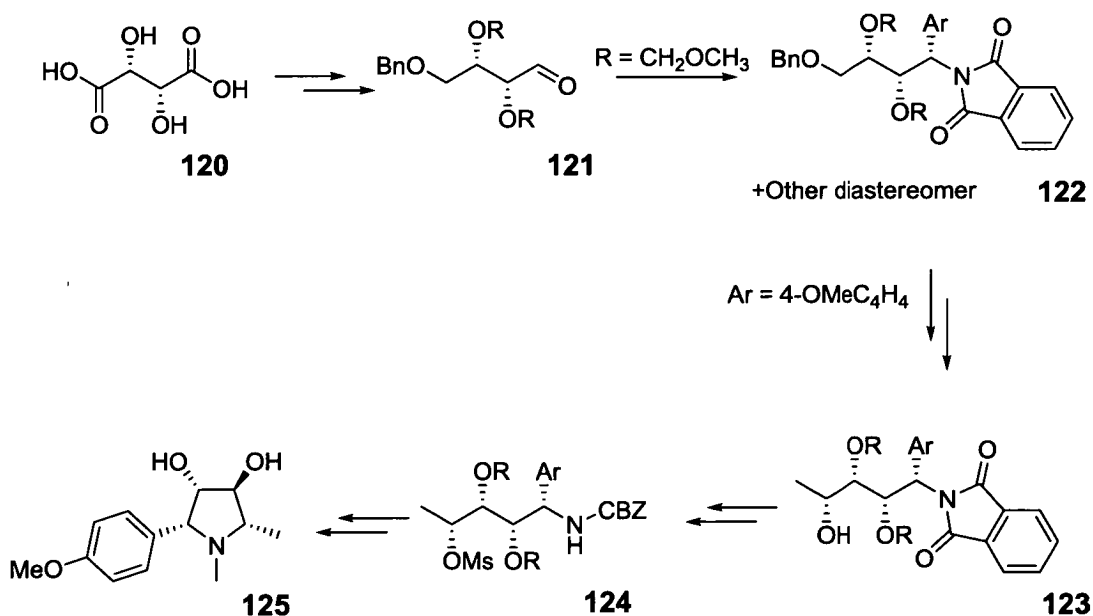
Daly also reported the identification of 2,5-dialkylsubstituted pyrrolidines as components in *anuran* skin extracts,³ where they are believed to be sequestered from their other known natural source, myrmicine ants.¹⁰²

Not only is the pyrrolidine moiety an important structural class of alkaloids in its own right, it is a core structure that is present in many bicyclic structures such as the aforementioned indolizidines, as well as pyrrolizidines.

2.2 Synthetic methods to pyrrolidine alkaloids

There have been numerous approaches to the synthesis of pyrrolidine natural alkaloids. Most of these approaches are extremely specific towards the synthesis of a particular alkaloid, and often lack flexibility to synthesise compound libraries.

The first total synthesis of (+)-codonopsinine was reported in 1985 by Kibayashi and co-workers, using L-tartaric acid **120** as the precursor for the carbon skeleton of the pyrrolidine ring, (Scheme 28).⁸⁸

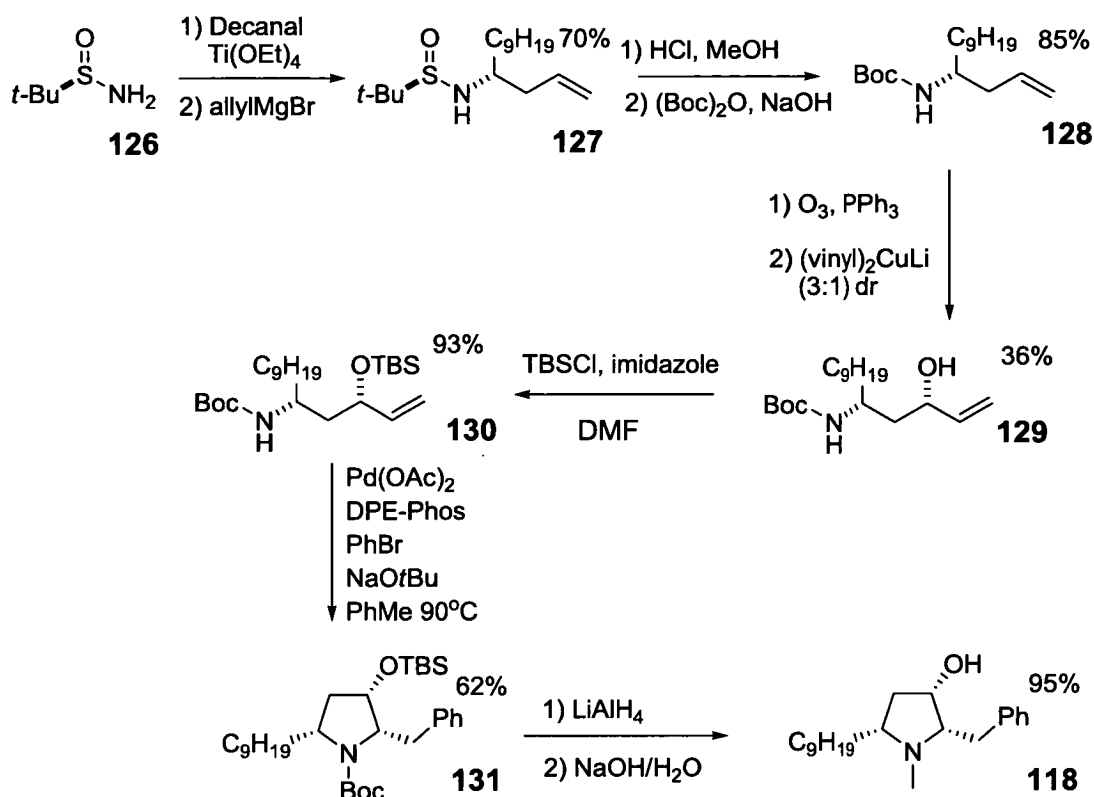


Scheme 28: Kibayashi's synthesis of (+)-codonopsinine.⁸⁸

The key steps in this synthetic approach were the treatment of aldehyde **121** with *para*-methoxyphenylmagnesium bromide to give a 3.3:1 mix of two diastereomers, which were converted, by a Mitsunobu reaction, to a separable 1:1 mixture of epimers **122**. Debenzylation of the appropriate epimer, followed by Swern oxidation and a chelation controlled addition of methyl Grignard gave product **123**. Protecting group manipulation and mesylation gave **124**, which underwent catalytic hydrogenolysis, *in situ* cyclisation, followed by *N*-methylation and alcohol deprotection to afford (+)-codonopsinine **125** in 16 steps and a 4% overall yield. A later report by Kibayashi corrected the structure of (+)-codonopsinine from **125** shown in Scheme 27, to (+)-**116** as he had incorrectly assigned the stereochemistry of **122**.⁸⁷ Kibayashi later prepared three other codonopsinine diastereomers by separation of minor diastereomers of **122** and elaborating these using the same method. In this manner, he was able to unequivocally determine the stereochemistry of natural (-)-codonopsinine.⁸⁹

Since this first synthesis many other approaches have been made towards the synthesis of codonopsinine.¹⁰³⁻¹⁰⁷

Preussin has also attracted a great deal of synthetic interest due to its interesting biological activity and challenging structure.¹⁰⁸⁻¹¹⁵ A recent approach from the group of Wolfe has allowed the enantioselective synthesis of preussin through incorporation of the aromatic ring by palladium catalysed carboamination of a protected amino alcohol, (Scheme 29).¹¹⁵ This method has facilitated the synthesis of a large library of preussin analogues through a common intermediate **130**, by varying the choice of aryl bromide utilised for the palladium-mediated coupling. This synthetic approach allows more extensive biological testing *via* SAR studies to take place.



Scheme 29: Wolfe's synthetic approach to (+)-preussin and its analogues.¹¹⁵

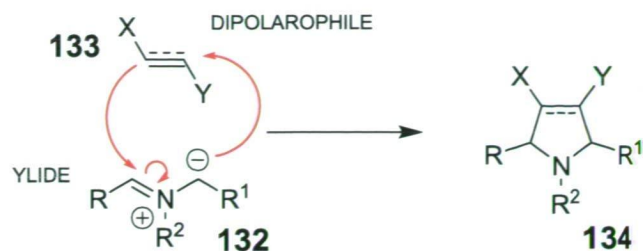
Wolfe's method resulted in the synthesis of the (+)-enantiomer of preussin starting from decanal. Addition of allyl Grignard reagent to a chiral sulfinylimine derived from decanal and **26**, gave a single diastereomer **127** upon purification. Removal of the chiral auxiliary then Boc protection of the amine gave **128**, which underwent ozonolysis to give a β -aminoaldehyde, followed by vinyl cuprate addition to give **129**. TBS protection of the alcohol of this intermediate gave **130**, which underwent palladium catalysed carboamination with phenyl bromide and sodium *t*-butoxide to yield **131**, followed by one-pot alcohol deprotection and *N*-Boc reduction to give **118** in 9 steps.

Thus, whilst there have been many different synthetic routes yielding naturally occurring pyrrolidine alkaloids found, as highlighted by the two examples given, these methods most commonly approach the target compound *via* synthesis of an amino intermediate with substituents in place, which can then utilise the nucleophilicity of the amine to undergo

cyclisation yielding the pyrrolidine core. Another common method to approach functionalised pyrrolidines is through the synthesis of 3,4-dihydropyrrole intermediates, then utilising the alkene as a handle to introduce functionality into the 3- and 4- positions of the pyrrolidine ring. One method for the generation of pyrrolidine rings that is not widely reported as an approach towards pyrrolidine alkaloids is the [3+2] cycloaddition chemistry of azomethine ylides. The benefit of such a route would stem from the ability to change substituents in the cycloaddition, leading to the ability to rapidly generate libraries of compounds. Hence, this approach became the focus of our investigation, determining the feasibility of developing methods utilising these cycloadditions to target highly functionalised pyrrolidine alkaloids such as codonopsinine.

2.3 Introduction to azomethine ylide chemistry

Azomethine ylide cycloadditions are a class of reactions that involve the [3+2] cycloaddition between an azomethine ylide and a dipolarophile. The azomethine ylides themselves are 1,3-dipoles containing one nitrogen and two sp^2 hybridised carbon atoms, best represented by the generic structure **132** below, (Scheme 30). Due to their high reactivity, azomethine ylides are typically generated *in situ*, and react with a dipolarophile **133** in a [3+2] cycloaddition to form a 5-membered nitrogen containing heterocycle such as a pyrrolidine **134**, or a 3-pyrroline if an acetylene is used as the dipolarophile. The use of intramolecular cycloadditions can lead to bicyclic and even more complex ring systems, as does the use of cyclic ylides or dipolarophiles. While these reactions can be viewed as a stepwise mechanism, studies have shown that the reaction most likely occurs as a concerted process, where the HOMO of the ylide interacts with the LUMO of the dipolarophile.¹¹⁶ This observation explains the key reactivity differences between various dipolarophiles, with dipolarophiles bearing electron-withdrawing substituents being the most reactive due to a lowering in energy of their LUMO.



Scheme 30: Generic azomethine ylide reaction.

Two main classes of ylide are known, stabilised and non-stabilised, where the former contains a functional group(s) that can stabilise the dipole charges, such as an aromatic ring or carbonyl group (Figure 10).

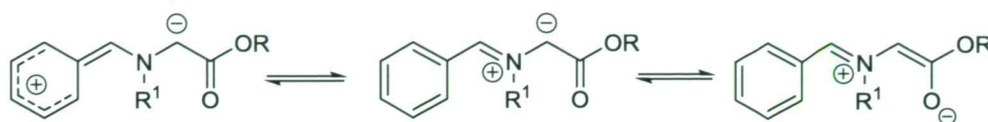


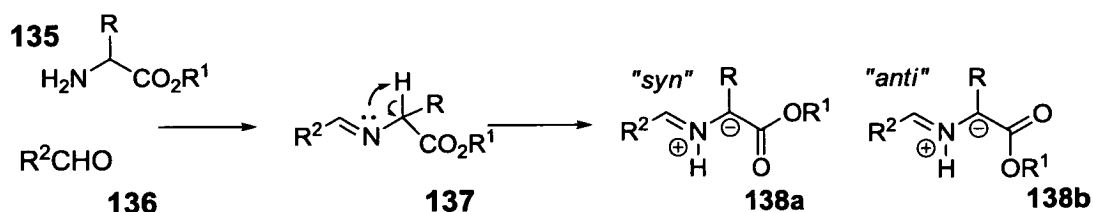
Figure 10: Resonance stabilisation of an azomethine ylide.

The review of Eberbach¹¹⁷ gives a good overview of the many methods utilised to generate azomethine ylides. These include cycloreversion of dihydro-1,2,4-triazoles and oxazolidines, as well as more straightforward techniques such as deprotonation of iminium salts. The three most studied methods for the generation of azomethine ylides are the methodologies that will be investigated towards the synthesis of pyrrolidine alkaloids in this thesis. These methods are the decarboxylation of iminium carboxylates, prototropic shift of an imine and desilylation of methoxy or cyanoaminosilanes.

Other reviews of note include Harwood and Vickers, who focus on the silicon mediated protocols for ylide generation, as well as discussing asymmetric and intramolecular cycloadditions.¹¹⁸ Pandey *et al.* have provided a comprehensive review of the synthesis of enantiopure pyrrolidines from azomethine methods.¹¹⁹

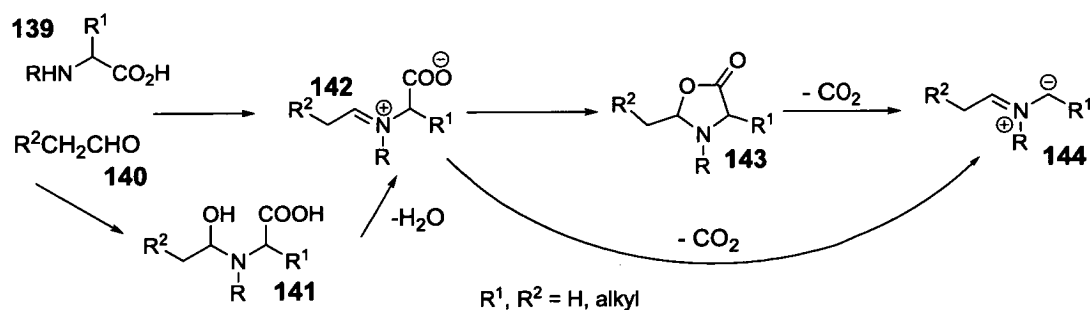
A frequently used method for the generation of stabilised azomethine ylides **138** is through prototropic shift of an imine **137**, (Scheme 31). Schiff bases of aromatic aldehydes are

commonly used as the imines in these reactions, as they are intermediates that under thermal or Lewis acid conditions undergo a prototropic shift to form the stabilised ylide **138**. The stabilised ylide can be formed from α -amino esters **135** and aromatic / heteroaromatic aldehyde derivatives **136**, leading to a wide variety of functional groups that can be introduced. The ylide **138** can also exist in two conformers, the "syn" (**138a**) and "anti" (**138b**) forms.



Scheme 31: Generation of a carbonyl stabilised ylide through prototropic shift.

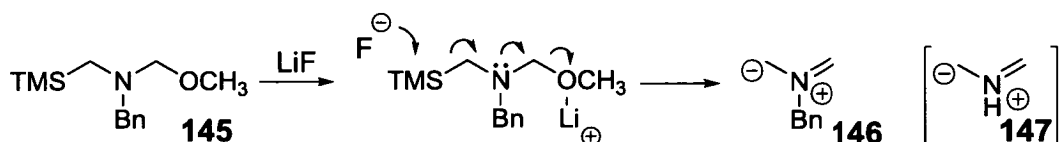
In the case of an amino acid **139** being utilised as a starting material, condensation with a carbonyl group **140** leads to the formation of an iminium carboxylate **142**, which in some cases is believed to undergo decarboxylation to form dipole **144**. However, Grigg showed that on the basis of stereochemical results that 1,3-oxazolidin-5-ones **143** are probable intermediates.¹²⁰ These 1,3-oxazolidin-5-ones have been shown to undergo cycloreversion and lose carbon dioxide at temperatures above approximately 100°C, which then yields the non-stabilised 1,3-dipole **144**, (Scheme 32).¹²¹



Scheme 32: Formation of a non-stabilised ylide through decarboxylation.

The drawback of the decarboxylative method for generation of azomethine ylides is that while many chiral α -amino acids are available from nature, the stereogenic centre is lost during formation of the ylide and therefore no chiral induction is possible.

A convenient method for the generation of azomethine ylides is that developed by Padwa, which involves fluoride-mediated desilylation of methoxy or cyanoaminosilanes **145** (Scheme 33).^{122,123} This method is utilised for the generation of non-stabilised azomethine ylide **146**, an excellent synthon for parent ylide **147**.



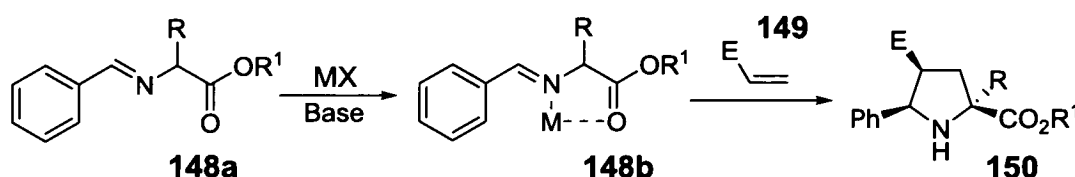
Scheme 33: Formation of a non-stabilised ylide from a methoxyaminosilane.

Whilst this is an effective method of generating simple azomethine ylides, there are very few examples of substituted derivatives known or available. Another method of desilylation has been reported by Achiwa,¹²⁴ and later utilised by Ryan,¹²⁵ in which the fluoride source is replaced simply by catalytic trifluoroacetic acid.

Thus, given the nature of the substituents in our target alkaloids, such as aromatic and alkyl groups, investigation into the synthesis of pyrrolidine alkaloids by azomethine methods started with generation of ylides from their corresponding imines *via* a prototropic shift, with the aryl at C2 coming from a benzaldehyde derivative and the substituent at C5 from the corresponding amino acid.

2.4 Fundamental studies into the application of azomethine ylides to the synthesis of pyrrolidine alkaloids

Extensive studies have been performed into the scope and reactivity of azomethine ylides for the construction of pyrrolidine ring systems. At the forefront of this fundamental research into the reactivity of these species has been Grigg and Tsuge, who have extensively reported using $X=Y-ZH$ compounds as 1,3-dipoles.⁷⁷ This study has extended from research into the fundamental generation of the ylides and their reactivity, to the generation of asymmetric polycyclic systems from azomethine ylides. In determining an appropriate approach to (-)-codonopsinine **118**, analysis of Grigg's body of work led us to investigate the chemistry he developed independently of, but simultaneously with the group of Tsuge, involving the use of *N*-metallated imines as a source of the ylide.^{126,127} Both developed diastereoselective azomethine ylide cycloaddition by chelation of a metal ion by the nitrogen and ester carbonyl group of imine **148**, formed from an α -amino ester and a benzaldehyde, which results in exclusive formation of the *syn* form of the ylide, a metallo-base, (Scheme 34). Both routes require an organic base to deprotonate the imine and form the *N*-metallated ylide. With the geometry of the ylide controlled, approach of the dipolarophile **149** occurs exclusively to the *endo* face of the ylide leading diastereoselectively to the *endo* adduct **150**. Tsuge utilised lithium salts to form his metallo-base whilst Grigg utilised a range of salts, preferring silver acetate to achieve the same result.

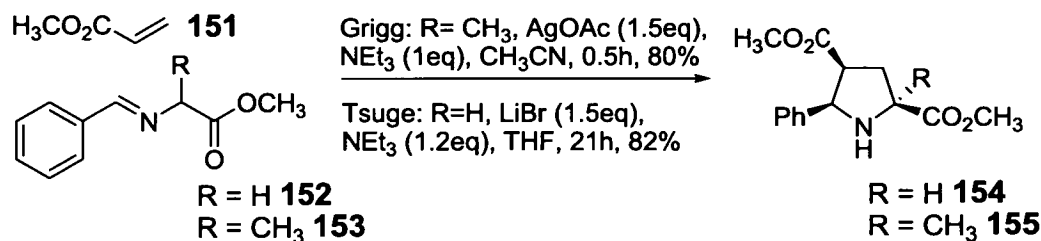


Scheme 34: Tsuge and Grigg's metallo-base controlled azomethine ylide cycloaddition.

Unfortunately, both of these reported methods have some downsides. While the method of Grigg is fast, it uses an excess of silver acetate, while Tsuge reports slow reaction, and

they both require a stoichiometric amount of base for optimal reactivity and yields.

Scheme 35 shows a comparison of both sets of conditions.



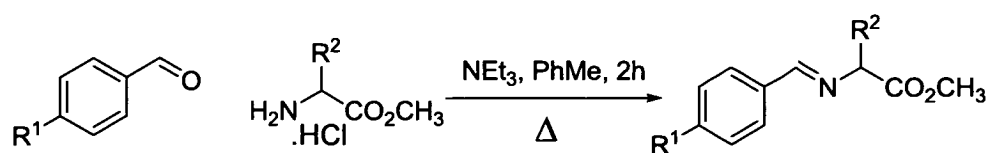
Scheme 35: Previously reported diastereoselective cycloaddition methods.^{126,127}

A range of electron deficient dipolarophiles were studied in these *N*-metallated reactions.

^{126,127} Thus, this work was taken as a starting point into developing azomethine ylide cycloaddition methods for the synthesis of pyrrolidine alkaloids; both through optimisation of the reaction conditions required to perform the *N*-metallated azomethine cycloadditions, such as the amount of base, (i.e. is catalytic base sufficient), and also through expanding the scope of these reactions by investigating the suitability of a greater variety of dipolarophiles to undergo these cycloadditions. The investigation into a wider range of dipolarophiles is required to develop a method for the introduction of oxygenated functionalities into the 3- and 4- positions of the pyrrolidine ring system, as is commonly encountered in the natural products.

2.4.1 Schiff Base synthesis

Therefore, the first step was the synthesis of the Schiff base imines. There are many methods for this simple condensation reaction,¹²⁷⁻¹³⁰ however, usually the starting materials and products form an equilibrium mixture. Various methods have been employed to remove water from the reaction and to drive the reaction towards completion. We decided to perform the condensation in refluxing toluene under Dean-Stark conditions as described by Tsuge, (Scheme 36).¹²⁷



R ¹	Benzaldehyde	R ²	Amino Ester	Imine	Yield
H	156	Me	161	162	>95%
Cl	157	H	160	163	>95%
Cl	157	Me	161	164	>95%
OMe	158	H	160	165	>95%
OMe	158	Me	161	166	>95%
NO ₂	159	H	160	167	>95%

Scheme 36: Schiff Base Synthesis.

A range of imines were formed by condensation reaction of benzaldehyde derivatives with electron donating and electron withdrawing groups (**156-159**) with the methyl ester hydrochlorides of glycine **160** or DL-alanine **161** to give the imines **162-167** in quantitative yield, (Scheme 36). The structure of the isolated imines was confirmed by comparison of the ¹H and ¹³C NMR spectra with that of the literature.^{127,131}

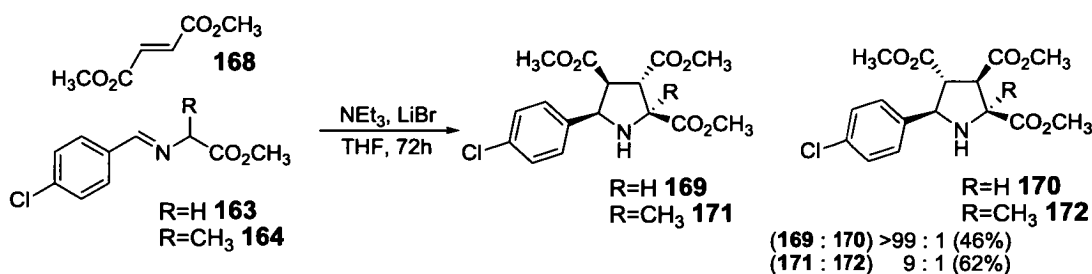
The defining characteristic in the ¹H NMR spectra of **162-167** was the absence of the signal of the aldehyde proton of **156-159** at approximately δ 10 ppm, and the presence of the imine proton resonance at approximately δ 8 ppm. Similarly, the ¹³C NMR spectra showed no aldehyde carbon resonances instead featuring imine signals at approximately δ 160 ppm.

2.4.2 Optimisation of the *N*-metallated azomethine ylide chemistry

As an initial investigation towards the synthesis of pyrrolidine alkaloids, we performed test cycloadditions between the *para*-chloro imines **163** and **164** and dimethyl fumarate **168** under both Tsuge's and Grigg's conditions. Analysis of the crude cycloaddition products

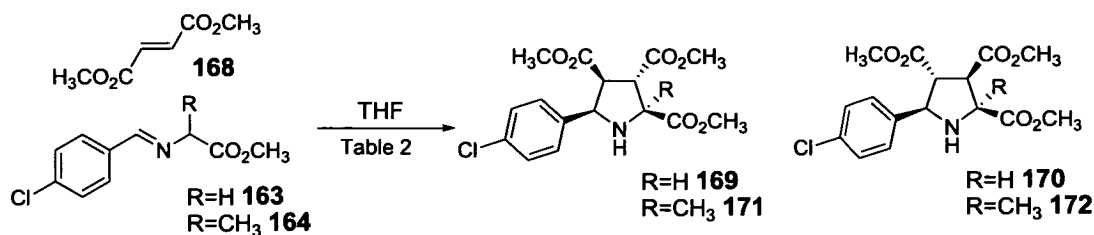
obtained indicated Tsuge's lithium bromide method gave cleaner reaction products than the method developed by Grigg, without the need for stoichiometric silver, (Scheme 37). Thus, we decided to optimise this lithium bromide based chemistry further.

As reported by Tsuge, the cycloadditions proceeded with high diastereoselectivity giving a single diastereomer in the case of the imine derived from glycine, however a 9:1 dr from the imine derived from alanine was observed, which was not reported by Tsuge, but was by Grigg on a similar substrate.¹²⁶



Scheme 37: Repeat of Tsuge's method.

Before developing an approach towards codonopsinine, investigation commenced into optimisation of Tsuge's conditions, both through optimisation of the base and metal salt, and also to investigate if shorter reaction times could be achieved. It was reasoned that if shortening of the reaction time was feasible, then yields may increase, as there is less chance for adventitious water to hydrolyse the imine. Tsuge reports that for the case of base sensitive dipolarophiles such as *N*-methylmaleimide and 3-buten-2-one, that catalytic amounts of base (0.1 equivalents) and lithium bromide are effective, with the only drawback being longer reaction times. Interestingly, he did not report the results of catalytic lithium bromide and base on any other dipolarophiles. The potential for epimerisation of the product pyrrolidines with the use of a base such as triethylamine is further cause to investigate the requirement of this reagent for cycloaddition, particularly if elevated temperatures are used to shorten the reaction time. Thus, the reaction variables were varied to determine optimum conditions for the cycloaddition using imines **163** and **164**, (Scheme 38, Table 2).



Scheme 38: Cycloaddition optimisation between imines **163** and **164** and dimethyl fumarate.

Entry	R	Temperature (°C)	NEt ₃ (Eq)	LiBr (Eq)	Reaction Time (h)	Yield (%)	Diastereoselectivity
1	CH ₃	r.t.	1	1.5	72	62	171:172 9:1
2	H	r.t.	1	1.5	72	46	169:170 >99:1
3	CH ₃	66	1	1.5	16	88	171:172 9:1
4	CH ₃	66	0	1.5	16	79	171:172 8:3
5	H	66	0	1.5	16	72	169:170 >99:1
6	CH ₃	66	0	0	16	0	N/A
7	CH ₃	66	0	0.2	16	<10	171:172 ≈9:1
8	CH ₃	110 (toluene)	0	1.5	6	≈85	171:172 1:2
9	CH ₃	70 (toluene)	0	1.5	6	0	N/A

Table 2: Scheme 37 reaction optimisation results.

In an attempt to shorten the three day reaction time originally reported by Tsuge, the reaction temperature was raised to 66°C, the boiling point of the solvent, THF.

Cycloaddition between alanine derived imine **164** and dimethyl fumarate in refluxing THF (entry 3), with base and lithium bromide gave an excellent yield of cycloadduct (88%) with no loss of diastereoselectivity compared to the room temperature reaction (entry 1). Diastereoselectivity was measured through integration of the C5 methine proton resonance at δ 4.76 and δ 4.39 ppm and the C2 methyl group resonances δ 1.36 and δ 1.64 ppm respectively, (Figure 11). As hypothesised, the yield of the reaction was noticeably increased by shortening the reaction time. Reaction of imine **164** at reflux without base, (entry 4), led to a good yield of cycloadduct (79%), however the diastereoselectivity of the reaction was lowered and an 8:3 ratio was obtained.

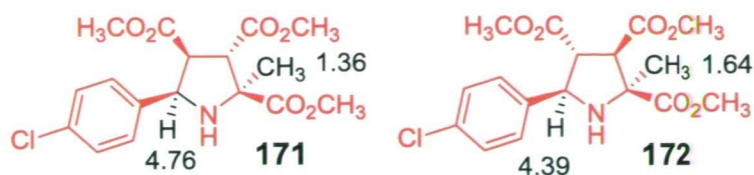


Figure 11: Distinguishing ¹H NMR shifts of **171** and **172**.

Conversely, reaction between glycine derived imine **163** and dimethyl fumarate at reflux without base, (entry 5), gave a 72% yield of cycloadduct, however as with the room temperature reaction (entry 2), only *endo* diastereomer **169** was observed by ¹H NMR spectroscopic analysis. Again the yield of cycloadduct was improved due to the shorter reaction time. These results appear to indicate that at increased temperature the methyl group of the alanine derived imine **164** hinders formation of a secondary chelation interaction between the lithium and the carbonyl group of the fumarate.

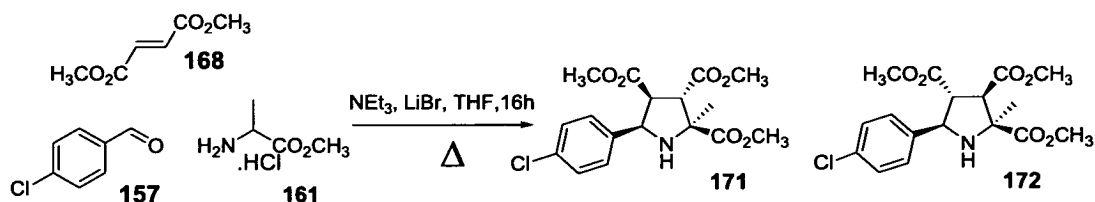
Reaction between **164** and dimethyl fumarate without the addition of lithium bromide or base, (entry 6), gave no cycloaddition, as evidenced by the lack of resonances for the methine protons of the C5 carbons of **171** and **172** at δ 4.76 and δ 4.39 ppm. Unreacted dimethyl fumarate was also not observed in the crude ¹H NMR spectroscopic analysis of the reaction, as no proton resonances were present at δ 6.83 ppm and δ 3.78 ppm; however a significant decomposition was apparent with the formation of signals between δ 1.6-2.0 and δ 3.5-4.0 ppm in the ¹H NMR spectrum of the crude reaction mixture. This led us to hypothesise that when dimethyl fumarate did not undergo cycloaddition, it slowly polymerised. This was confirmed by heating a sample of dimethyl fumarate in THF for 16h. ¹H NMR spectroscopic analysis showed resonances at δ 1.6-2.0 and δ 3.5-4.0 ppm, supporting that no reaction with an azomethine ylide was occurring.

Cycloaddition between **164** and dimethyl fumarate in refluxing THF, with a catalytic amount of lithium bromide and no base, led to a negligible amount of cycloaddition, (entry 7). In this case the product was not isolated and the yield, <10%, was estimated through integration of the benzylidene proton of the imine *versus* the integration of the C5 methine

protons of the cycloadducts. Only *endo* cycloadduct **171** was visible by ^1H NMR spectroscopic analysis; however the low level of cycloaddition would hinder the visualisation of the minor isomer in the crude product.

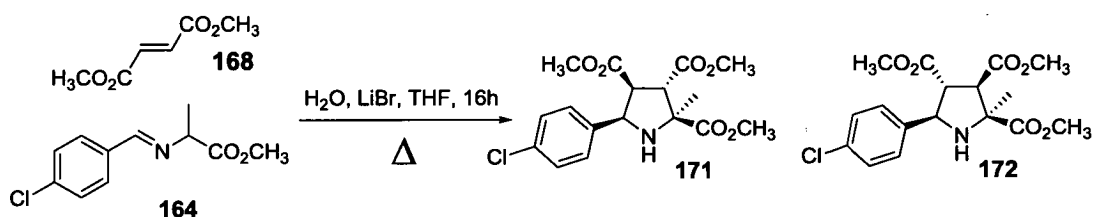
Raising the reaction temperature in an attempt to further decrease the reaction time by heating **164**, dimethyl fumarate and lithium bromide in refluxing toluene gave a high yield of a 1:2 ratio of diastereomeric pyrrolidines **171** : **172**, where the previously minor isomer was now the major product, (entry 8). The ratio of diastereomers was obtained by integration of the C5 methine protons at δ 4.76 and δ 4.39 ppm and the C2 methyl resonances at δ 1.36 and δ 1.64 ppm. To determine if the reversal in diastereoselectivity was due to a loss of chelation of the lithium as a result of increased temperature, or if the lithium bromide was too insoluble in toluene to form a chelate (visible inspection of the reaction suggested this to be a factor). The reaction was repeated in toluene at 70°C, (entry 9), a similar temperature to the reactions in THF. At this temperature there was no reaction, therefore indicating that at higher temperature the ylide is mostly being formed *via* thermal prototropic shift, and that it is still the *syn* form of the azomethine ylide that reacts. However, without lithium chelation, a lack of facial selectivity and greater amounts of the *exo* isomer result.

To further the investigation, the requirement for the pre-formation of the imine was determined by studying the effect of forming the imine *in situ*. Heating a mixture of DL-alanine methyl ester hydrochloride, one equivalent of triethylamine to liberate the amine from the salt, *para*-chlorobenzaldehyde, lithium bromide and dimethyl fumarate in THF for 16h showed evidence of cycloaddition, however under these reaction conditions the two diastereomers (**171**, **172**) were formed in an approximately 1:1 ratio, (Scheme 39). ^1H NMR analysis indicated an approximately 60% yield of cycloadduct through integration of the combined C5 methine protons vs. unreacted dimethyl fumarate.



Scheme 39: Cycloaddition with no pre-formation of imine.

To determine if the loss of stereochemistry was due to the water released in the condensation to form the imine interfering with the chelation of the lithium, a reaction was performed under the previously optimised anhydrous conditions, but with one equivalent of water added, (Scheme 40).



Scheme 40: Cycloaddition with an equivalent of water.

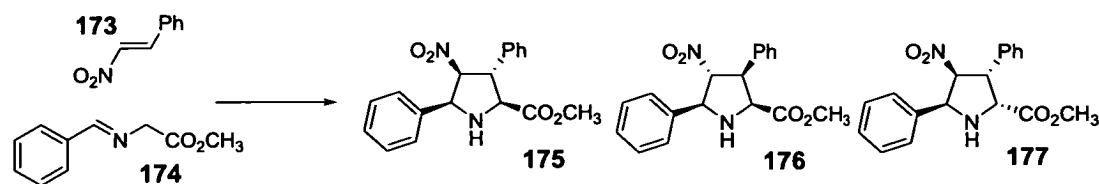
Confirming the belief that the water interfered with the lithium chelation, a 1:1 mixture of diastereomers was again found, as evidenced by the integration of the pair of doublets at δ 4.76 and 4.39 ppm representing the C5 methine proton of each diastereomer. This therefore indicated that water can hinder the chelation of lithium, and that imines should be pre-formed. An alternative method may be to use molecular sieves to remove the H_2O formed in the imine condensation *in situ*, but this was not investigated.

These results suggest that the optimal reaction conditions strongly depend on both the ylide and dipolarophile, however lithium chelation can be maintained at elevated temperatures, and hence reaction times can be shortened from those reported by Tsuge.¹²⁷

2.4.3 Microwave assisted azomethine ylide cycloaddition

Given the favourable results obtained by increasing the cycloaddition reaction temperature utilising refluxing tetrahydrofuran, further shortening the reaction time through the use of microwave assisted chemistry was investigated. Microwave chemistry is a relatively new field, and is being extensively researched and applied to different chemistries because of the significant advantages it can offer over traditional techniques. A good review highlighting the benefits and applications of microwave assisted synthesis has been compiled by Nüchter *et al.*¹³² It is most widely utilised to shorten reaction times, as the reactions are generally performed under pressure in sealed reaction vessels at temperatures above the boiling point of the solvent, allowing for an approximately 50% reduction in reaction length for every 10°C increase in temperature.¹³³

There has so far been little investigation into microwave-assisted azomethine ylide chemistry. However, a recent experimental and theoretical study by Cossio¹³⁴ investigated the outcomes of [3+2] cycloadditions between stabilised azomethine ylides formed by prototropic shift and nitrostyrene under thermal and microwave-assisted conditions. They found that solvent-free microwave irradiation at 120°C in an open vessel generated cycloaddition adducts in shorter reaction times (10 – 15 min vs. 24h) and improved yields (81-87% vs. <60%) over refluxing in toluene as reported previously.¹³⁵ However they also reported the formation of a third isomer not observed when refluxing toluene was utilised, (Scheme 41).

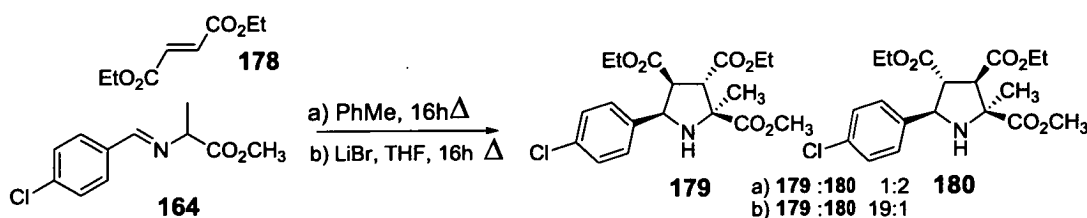


Conditions	Yield (%)		
	175	176	177
Toluene, Δ	21	41	0
μ wave, 120°C, neat	33	37	17

Scheme 41: Cossio microwave vs. thermal cycloaddition to nitrostyrene.^{134,135}

Interestingly when Cossio heated imine **174** and nitrostyrene **173** under classical thermal conditions in the absence of solvent, stereoisomer **177** was again observed through crude ^1H NMR spectral analysis, indicating toluene plays a role in the stereochemical outcome of the reaction.

Thus we decided to investigate the use of microwave radiation for diastereoselective cycloaddition between alanine derived imine **155** and diethyl fumarate. Prior to microwave cycloaddition, both the *endo* and *exo* cycloadducts of diethyl fumarate were obtained under thermal heating conditions for spectral comparison. Refluxing **164** and diethyl fumarate (**178**) in toluene under Dean-Stark conditions for 16h gave a 2:1 mixture of *exo* and *endo* cycloadducts **179** and **180** in 77% yield. Refluxing **164**, diethyl fumarate and lithium bromide in tetrahydrofuran for 16h gave almost exclusively *endo* cycloadduct **179** in a 52% yield, (Scheme 42).

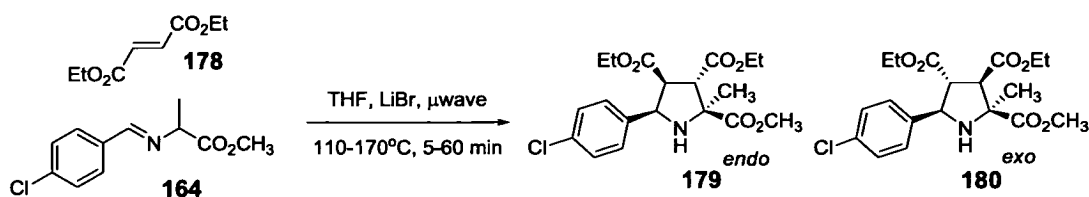


Scheme 42: Diethyl fumarate comparison reaction.

Stereochemical assignment of the cycloaddition products **179** and **180** was inferred from comparison of their ^1H NMR spectra to the dimethyl fumarate analogues **171** and **172**. The key spectroscopic identifiers between the two pyrrolidines were the doublet resonances in their ^1H NMR spectra for the C5 protons adjacent to the aromatic ring. For *exo* isomer **180** the C5 methine proton resonated at δ 4.48 ppm, whereas for the *endo* isomer **179** the corresponding proton resonated at δ 4.81 ppm.

Interestingly, reaction between **164** and diethyl fumarate with lithium bromide in the absence of base gave a higher diastereoselectivity when compared to the analogous dimethyl fumarate reaction. In the ^1H NMR the integration ratio between the *endo* and *exo* C5 methine protons was in excess of 95:5 as no other *exo* isomer protons were visible. In the ^{13}C NMR the *exo* diastereomer **180** carbon resonances could not be distinguished from spectral noise.

With this NMR spectral data for comparison, imine **164**, lithium bromide and diethyl fumarate in THF were heated using a Biotage microwave reactor in a 2-5mL vial, pre-stirred for 30 seconds then controlled to a set temperature, using variable microwave power for the fixed times reported in table 3. The *endo/exo* cycloaddition selectivity was determined by analysis of the crude ^1H NMR spectra, through the integration ratio of the C5 methine protons and the C2 methyl group resonances at δ 0.86 and δ 1.12 ppm. The yield was determined through the comparison of the integration of the C5 protons compared to unreacted diethyl fumarate, (Scheme 43, Table 3).



Scheme 43: Microwave conditions optimisation.

Temperature (°C)	Time (min)	Yield (%)	Endo 179	Exo 180
110	60	60	1	2
130	45	>95	1	2
130	15	75	1	2
150	10	90	1	2
170	5	90	1	2

Table 3: Scheme 40 reaction optimisation results.

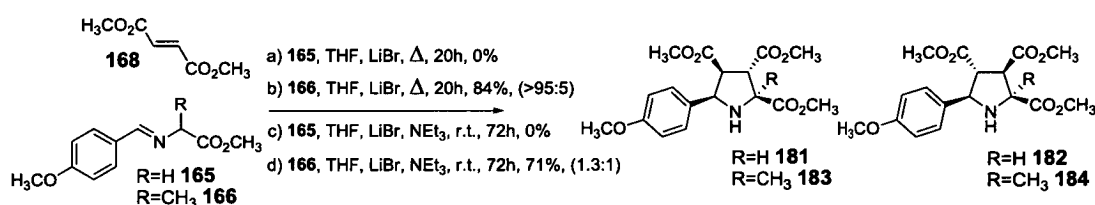
Unfortunately at all temperatures under microwave irradiation, the *endo/exo* cycloaddition selectivity was the same as obtained under the conventional conditions of refluxing toluene, which forms the ylide through prototropic shift, indicating the thermodynamic product distribution was obtained. This clearly shows that the ability of the lithium to chelate the nitrogen and the carbonyl group and control the imine conformation is lost at higher temperatures, and below 100°C the rate is not sufficiently enhanced over refluxing THF.

The ability of microwave irradiation to shorten reaction times, as previously demonstrated by Cossio, was confirmed. However, the loss of diastereoselectivity meant that microwave irradiation was unable to further enhance our optimisation of Tsuge's reaction conditions. The use of microwave irradiation in studies into cycloaddition of less activated dipolarophiles will be discussed later.

2.4.4 Substituted imines – *para*-methoxy

As the C2 substituent of our target alkaloid codonopsinine bears a *para*-methoxy substituted phenyl ring, the reactivity of the more electron-rich imines **165** and **166** derived from anisaldehyde was investigated for cycloaddition using our modified Tsuge conditions. Cycloaddition reactions with imines **165** and **166** have not been reported utilising Tsuge's LiBr method, however Grigg reported the cycloaddition of **165** through an intramolecular route after an initial Michael reaction with divinyl sulfone.¹³⁶

In tetrahydrofuran, imines **165** and **166** were reacted with dimethyl fumarate and lithium bromide at reflux, and with dimethyl fumarate, lithium bromide and triethylamine at room temperature, (Scheme 44).



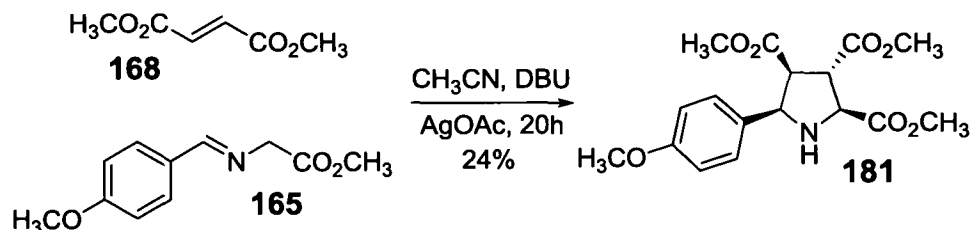
Scheme 44: Cycloadditions of *para*-methoxyphenyl substituted imines with dimethyl fumarate.

Surprisingly the reaction between dimethyl fumarate and imine **165** under both Tsuge's original and our reflux conditions showed no evidence of cycloaddition by analysis of the ¹H NMR spectra of the crude reaction mixtures. However, reaction of the analogous alanine derived imine **166** at room temperature with base gave almost exclusively the *endo* diastereomer **183**, with a >95 : 5 mixture of inseparable diastereomeric cycloadducts **183** and **184** isolated. The spectral assignment was determined from the ¹H NMR spectrum of the mixture of cycloadducts, and comparison to the analogous *para*-chloro derivatives **171** and **172**. The major diastereomer **183** was observed through its diagnostic C5 methine proton resonance at δ 4.74 ppm and C2 methyl group resonance at δ 1.35 ppm. Also observed in the ¹H NMR spectrum was a doublet at δ 4.30 ppm (J = 8.2 Hz) and a singlet at δ 1.61 ppm assigned as the corresponding resonances of the minor diastereomer **184**.

Integration of the diagnostic resonances of each diastereomer indicated the major *endo* isomer consisted of over 95% of the mixture, and in the ^{13}C NMR the minor isomer could not be distinguished from the baseline noise.

Cycloaddition at reflux in the absence of base gave an 84% yield of cycloadducts **183** and **184** as a 1.3 : 1 mixture of diastereomers respectively. This result was similar to the reaction of *para*-chloro imine **164** with dimethyl fumarate in the absence of base, indicating that the methyl group of the ylide interferes with chelation of the dimethyl fumarate controlling the facial selectivity of the cycloaddition. The ^1H and ^{13}C NMR spectra of the mixture were analogous to that obtained for the *para*-chloro imine series.

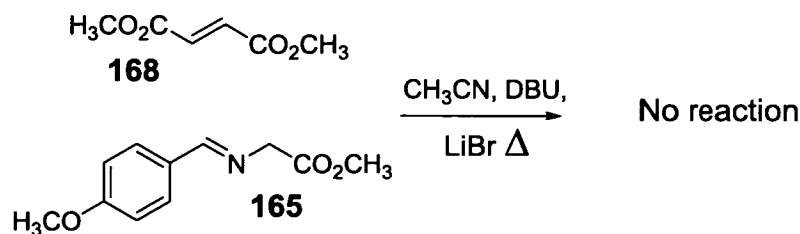
Given the LiBr mediated cycloaddition conditions were unable to achieve cycloaddition between imine **165** and dimethyl fumarate, the reaction was attempted using Grigg's silver acetate mediated method, and under these conditions gave a 24% yield of cycloadduct **181** as a single diastereomer, (Scheme 45).



Scheme 45: Cycloaddition of imine **165** and dimethyl fumarate using Grigg's method.

Stereochemical assignment of **181** was determined by spectroscopic analysis of the ^1H NMR spectrum compared to *para*-chlorophenyl pyrrolidine **169**, however in this case, the aromatic resonances were visible as two doublets at δ 7.54 and δ 8.17 ppm instead of collapsing to a multiplet as for **169**. Clearly this imine shows a reduced reactivity towards azomethine cycloaddition when compared to the alanine derived analogue **166**, or those derived from *para*-chlorobenzaldehyde.

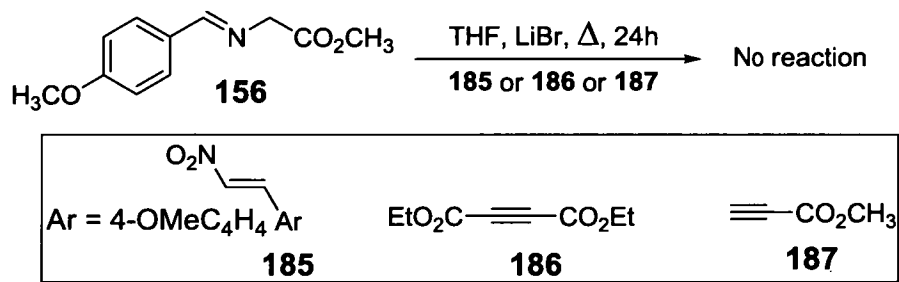
Given the limited success of the silver acetate mediated reaction, cycloaddition of **165** with dimethyl fumarate was attempted with lithium bromide using the alternative solvent and stronger base DBU, (Scheme 46).



Scheme 46: Attempted LiBr mediated cycloaddition of **156**.

In this case there was extensive hydrolysis of the imine, leading to the observation of anisaldehyde in the ^1H NMR spectrum of the crude reaction mixture, with no indication of pyrrolidine formation.

To further investigate the reactivity of *para*-methoxyphenyl imine **165**, cycloaddition was attempted with 4-methoxy nitrostyrene **185**, diethyl acetylenedicarboxylate **186** and methyl propiolate **187** as dipolarophiles, (Scheme 47).

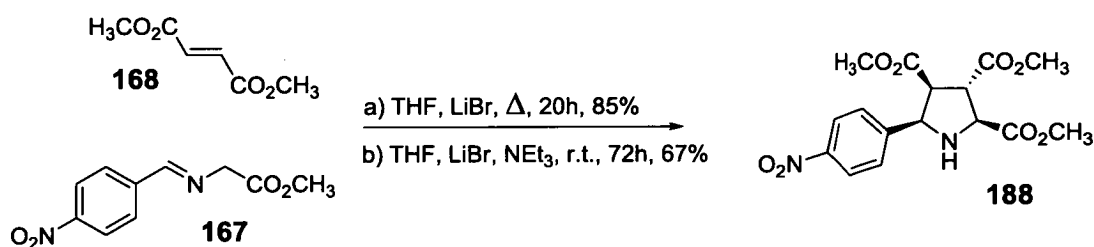


Scheme 47: *para*-Methoxy imine dipolarophile investigation.

In each case, reaction between imine **165** and dipolarophile in refluxing THF with lithium bromide gave no observable cycloadduct formation, as determined after aqueous work up by analysis of their crude ^1H NMR spectra, with unreacted imine **165** and its hydrolysis product anisaldehyde isolated. Again, addition of base with nitrostyrene did not promote any reaction, but was not attempted for **186** and **187** due to potential for polymerisation.

Dipolarophile decomposition was also noted in each reaction with no observable traces of dipolarophile remaining after workup.

To further investigate if the lowered reactivity of imine **165** was an electronic effect due to the electron rich substituent on the phenyl ring, the *para*-nitrophenyl imine **167** was examined, (Scheme 48). Reaction of imine **167**, dimethyl fumarate and lithium bromide in refluxing THF gave an 85% yield of **188** as a single diastereomer. Reaction at room temperature with triethylamine gave a 67% yield of cycloadduct, indicating that the substituent on the aryl ring can have a marked effect on the rate of cycloaddition. These yields compare with 72% and 46% for the analogous reaction at reflux and room temperature respectively, for the *para*-chlorophenyl imine **163**.



Scheme 48: Cycloaddition of *para*-nitro imine **158**.

Stereochemical assignment of **188** was performed by comparison to the *para*-chloro derivative **169** and the *para*-methoxy derivative **181**. As with **181**, the aromatic proton resonances were visible as a pair of doublets, at δ 8.17 and δ 7.54 ppm, instead of collapsing to one signal as in the *para*-chloro case **169**. All other proton signals were slightly shifted compared to their *para*-chloro counterparts, but coupling constants were consistent, and therefore we have assigned the same relative stereochemistry.

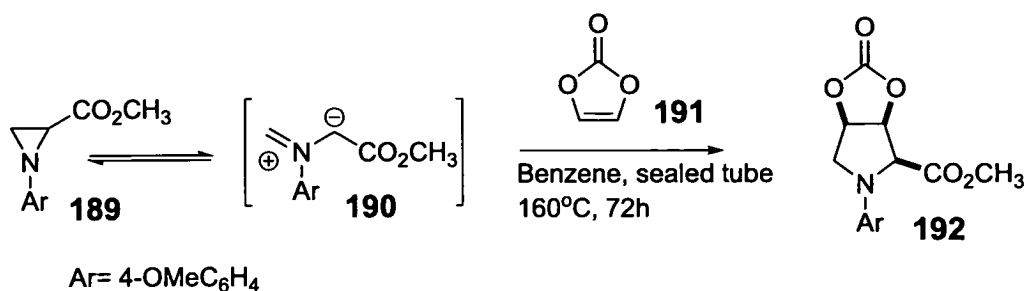
With the discovery of this interesting reactivity difference between the ylides formed from various imines, research moved to investigating the use of a variety of dipolarophiles.

2.4.5 *N*-Metallated azomethine ylide dipolarophile investigation

Tsuge has investigated the reactivity of a range of dipolarophiles with *N*-lithiated azomethine ylides, from highly active maleimides and fumarates, to less activated acrylates and α,β -unsaturated ketones.¹²⁷ All of these dipolarophiles are electron-deficient olefins, and are thus highly reactive in normal electron demand cycloadditions due to the low energy of their LUMO which allows a good overlap with the HOMO of the azomethine ylide and consequent cycloaddition. However, given the target compounds are hydroxylated pyrrolidine alkaloids, cycloaddition to dipolarophiles with oxygen functionality was investigated. These dipolarophiles are generally less reactive, however the increased temperature of our modified cycloaddition system compared to Tsuge's was tested to determine if cycloaddition could occur under these conditions.

2.4.5.1 Vinylene carbonate

One potentially useful dipolarophile for the synthesis of hydroxylated pyrrolidines is vinylene carbonate **191**. Because of the electron-donating nature of the substituents of the alkene, it is not highly active towards cycloadditions with azomethine ylides due to increased LUMO energy of the electron-rich vinylene carbonate, which results in a large difference in the dipolarophile LUMO – azomethine ylide HOMO gap. Despite this potential lack of reactivity, DeShong has provided a single report on the use of this dipolarophile with an azomethine ylide (**190**) generated through thermal ring opening of an aziridine (**189**), however this did require forcing conditions of 160°C for 3 days, (Scheme 49).¹³⁷



Scheme 49: DeShong's aziridine generated azomethine ylide cycloaddition to vinylene carbonate.¹³⁷

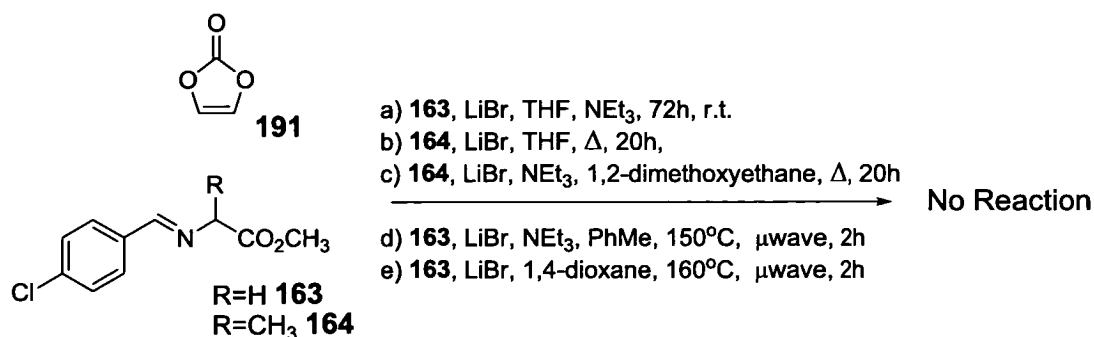
To test if this dipolarophile would react with a stabilised azomethine ylide formed from an imine, we tried a variety of reaction conditions, (Scheme 50).

Reaction using Tsuge's original conditions between imine **163**, vinylene carbonate, triethylamine and lithium bromide at room temperature for 72h, gave no evidence of cycloaddition as determined by crude ¹H NMR spectrum analysis. Vinylene carbonate was not isolated from the reaction, as the resonance for the alkene protons of vinylene carbonate at δ 7.15 ppm was not observed, indicating decomposition had occurred. Imine **163** was recovered, evidenced by the alkylidene proton at δ 8.22 ppm, however the majority of the imine had hydrolysed, presumably upon workup, as shown by the aldehydic proton at δ 9.95 ppm.

Given cycloaddition was not achieved at room temperature; vinylene carbonate and imine **164** were heated in refluxing THF with lithium bromide. ¹H NMR analysis of the crude reaction mixture again indicated no cycloaddition had occurred and that vinylene carbonate had decomposed.

The temperature of the reaction was further increased by heating vinylene carbonate, **164**, LiBr in refluxing 1,2-dimethoxyethane (85°C), and triethylamine was added to catalyse the reaction. Again, analysis of the ¹H NMR spectrum of the crude reaction mixture showed no cycloaddition had occurred. Unreacted dipolarophile was isolated from the reaction,

suggesting accelerated rates of decomposition in tetrahydrofuran; however no imine remained as it had all hydrolysed to aldehyde.



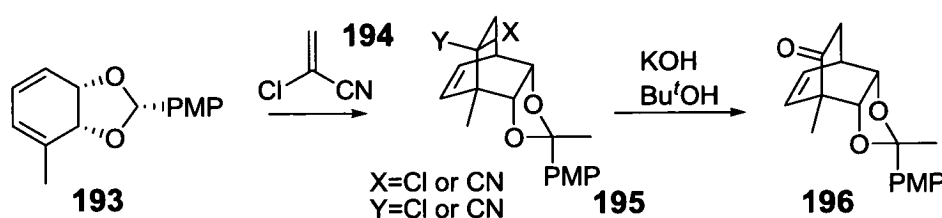
Scheme 50: Attempted use of vinylene carbonate as a dipolarophile.

Given DeShong's report of cycloaddition utilised a temperature of 160°C, as a further test to attempt cycloaddition, reactions were attempted in closed tubes with microwave irradiation. Heating vinylene carbonate, **163**, lithium bromide and triethylamine in toluene for 2h in a microwave using 300W of power achieved a maximum temperature of 150°C, which after workup showed decomposition of the dipolarophile through ¹H NMR analysis. To further increase the reaction temperature, the solvent was changed to 1,4-dioxane, and silicon carbide was added to the flask. Silicon carbide is an inert compound known to absorb microwave radiation, and is used to increase the temperature of microwave reactions when the reagents and solvent do not strongly absorb.¹³⁸ However, the reaction temperature still only reached 160°C and after 2 hours no cycloaddition products were observable by ¹H NMR analysis, with vinylene carbonate again decomposing.

Thus, given no apparent method for performing cycloaddition of vinylene carbonate with a stabilised ylide, alternative methods for introducing oxygenated functionality were investigated.

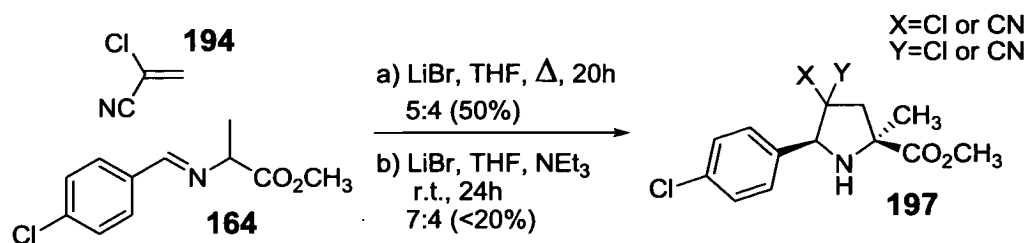
2.4.5.2 Ketene Equivalents

Another potential route to the introduction of oxygenated functionality into the 3 or 4 positions of the pyrrolidine rings is through the use of a ketene equivalent. These have been extensively studied in Diels-Alder chemistry, and two commonly-used reagents, 2-chloroacrylonitrile and phenyl vinyl sulfone, were investigated. A recent example from Banwell in his efforts to synthesise taxinine involved Diels-Alder addition of 2-chloroacrylonitrile **194** to a substituted cyclohexadiene **193**, yielding adduct **195**, which underwent hydrolysis to give the ketone **196** in 86% yield over two-steps, (Scheme 51).¹³⁹



Scheme 51: Banwell's use of chloroacrylonitrile as a ketene equivalent.¹³⁹

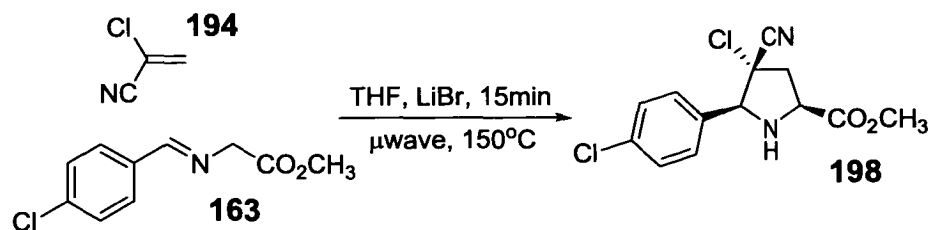
Our initial investigation commenced with the cycloaddition of imine **164**, 2-chloroacrylonitrile **194** and LiBr in refluxing THF, (Scheme 52). This reaction gave a mixture of *endo* and *exo* diastereomers **197** as a 5:4 ratio in a 50% yield. This was determined from integration of the ¹H NMR singlets at δ 4.48 and δ 4.69 ppm assigned as the methine proton adjacent to the aromatic ring of each diastereomer. The methylene protons at C3 were also clearly identified for each diastereomer, exhibiting as doublets at δ 3.50 and δ 2.46 ppm, and δ 3.27 and δ 2.68 ppm, with geminal coupling constants of 13.5Hz in each case. At this point assignment of the major and minor diastereomers could not be made, however hydrolysis of each diastereomer would yield the same ketone product.



Scheme 52: 2-Chloroacrylonitrile cycloaddition studies.

As Tsuge did not report investigation of this dipolarophile, reaction of **164**, 2-chloroacrylonitrile, lithium bromide and triethylamine in THF at room temperature was performed. Visual inspection of the reaction indicated that in the presence of base the dipolarophile was undergoing significant levels of decomposition. Therefore, after 24h the reaction was worked up, and inspection of the crude reaction mixture by ¹H NMR spectroscopy showed a 7:4 ratio of diastereomeric pyrrolidines had been obtained, presumably favouring the *endo* isomer, as a higher selectivity would be expected at lower temperature. However, spectroscopic analysis indicated the major isolated material was unreacted imine, with a small amount of 2-chloroacrylonitrile observed. Integration indicated a cycloaddition yield of less than 20% was obtained. A test reaction of 2-chloroacrylonitrile and triethylamine in THF confirmed that a side reaction with the base was occurring, and this highlights an important restriction of the methods of Tsuge and Grigg in that both use a base. We have shown that this can be overcome by increasing the temperature of the cycloaddition with only the addition of LiBr.

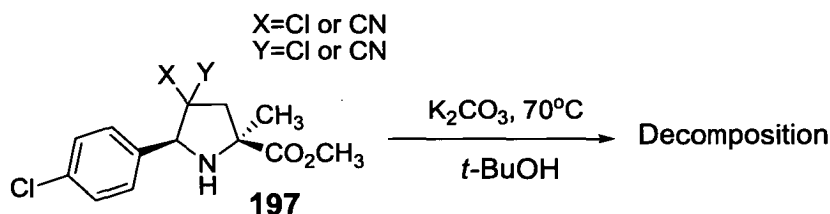
Cycloaddition of imine **163** and 2-chloroacrylonitrile **194** was also investigated in a sealed tube at 150°C using microwave radiation, (Scheme 53). Interestingly, this reaction showed only one diastereomer upon analysis of the crude ¹H NMR spectrum, and after isolation a 25% yield of **198** was obtained. Dr Roger Mulder of CSIRO deduced the relative stereochemistry of **198** using long range HSQC experiments, which determined the relationship between the nitrile and the aryl groups as *syn*.



Scheme 53: Microwave use of chloroacrylonitrile as a dipolarophile.

Again, the methine proton adjacent to the aromatic ring was diagnostic at δ 4.53 ppm, and the methylene protons at C3, as with **197**, showed geminal coupling of 14 Hz, as well as the vicinal couplings of 6.5 and 8.6 Hz to the C2 proton.

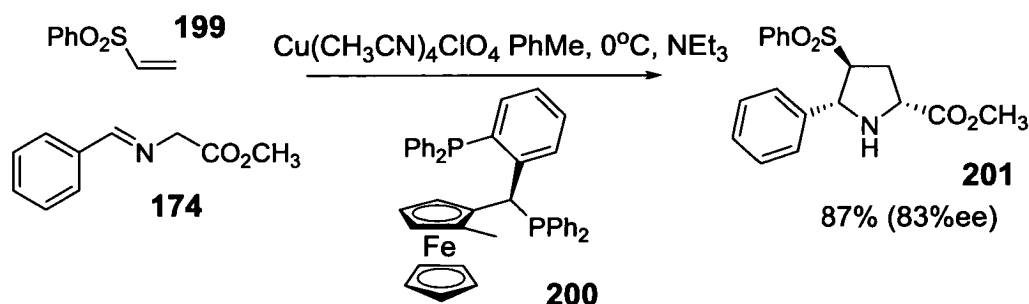
Attempted hydrolysis of the mixture of diastereomeric α -chloronitrile pyrrolidines **197** using the method reported by Banwell, (heating with potassium carbonate in *t*-butanol) gave no observable 3-pyrrolidinone formation, (Scheme 54).¹³⁹



Scheme 54: Attempted hydrolysis of α -chloronitrile pyrrolidines **178**.

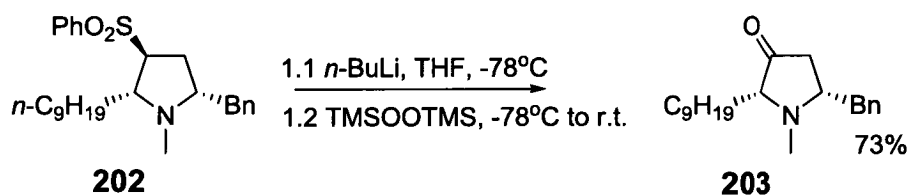
^1H NMR spectral analysis of the crude reaction mixture showed that significant decomposition of the pyrrolidine or the hydrolysis product had occurred. Whilst the desired 3-pyrrolidinone was not isolated, Pei reported the hydrolysis of an α -chloronitrile in the presence of an *N*-benzylamine on an azabicyclo[3.2.1]octane derivative gave only 35% of the desired ketone.¹⁴⁰ Thus, due to the presence of the amine, the hydrolysis adducts appear to be unstable. Therefore, phenyl vinyl sulfone was investigated to determine if it was a viable ketene equivalent. Future work could investigate protecting the pyrrolidine amine prior to hydrolysis with an electron withdrawing group such as a benzyloxycarbonyl group.

Unlike 2-chloroacrylonitrile, phenyl vinyl sulfone (**199**) has been utilised many times in azomethine reactions,^{137,123,121,141} including by Tsuge in his studies into decarboxylative cycloadditions,^{121,142} and recently by Carretero in enantioselective studies of phosphine ligands with Cu^I catalysis, (Scheme 55).¹⁴³



Scheme 55: Carretero's chiral use of phenyl vinyl sulfone.¹⁴³

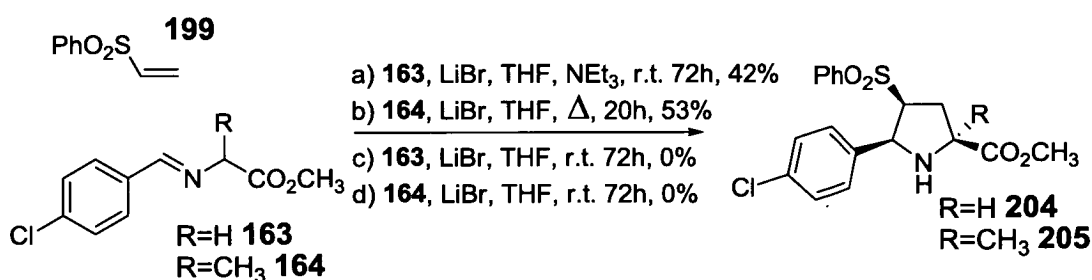
Carretero tested a variety of phosphine ligands, and managed to achieve asymmetric induction up to 83% ee for the cycloaddition of **199** to imine **174** with a chiral ferrocene derivative (Taniaphos) **200**.¹⁴³ Carretero also reported the desulfonation of pyrrolidine **201** with sodium amalgam, thus phenyl vinyl sulfone represents an ethylene equivalent for cycloaddition reactions.¹⁴³ A recent report by Craig detailing the synthesis of preussin **118** described a method for the transformation of the phenylsulfonyl pyrrolidines into their corresponding keto-derivatives, (Scheme 56).¹¹²



Scheme 56: Craig's use of phenyl sulfonyl moiety as a ketone precursor.¹¹²

Craig elaborated phenylsulfonylmethane to the pyrrolidine derivative **202**, before employing an oxidative desulfonation of the corresponding sulfonyl-stabilised carbanion to yield ketone **203**. Thus, if phenyl vinyl sulfone can be utilised as a dipolarophile to synthesise pyrrolidines similar to this, it could become an important tool as a ketene equivalent for the synthesis of pyrrolidine natural products *via* azomethine methodology.

As cycloaddition between phenyl vinyl sulfone and a stabilised ylide generated using Tsuge's LiBr conditions had not been reported, we investigated cycloaddition at room temperature and at reflux, (Scheme 57). Reaction between imine **163** and phenyl vinyl sulfone with lithium bromide and triethylamine at room temperature for 72h led to isolation of cycloadduct **204** in a 42% yield. ^1H NMR analysis indicated formation of **204**, as evidenced by the doublet resonating at δ 4.74 ppm diagnostic for the proton at C5 adjacent the aromatic ring with coupling constant 5.8 Hz. The low yield of cycloaddition was most likely due to the low reactivity of the dipolarophile, with ^1H NMR analysis prior to purification indicating a large portion of unreacted phenyl vinyl sulfone and imine remaining. Therefore the yield should be improved by increasing reaction time, or increasing the reaction temperature.



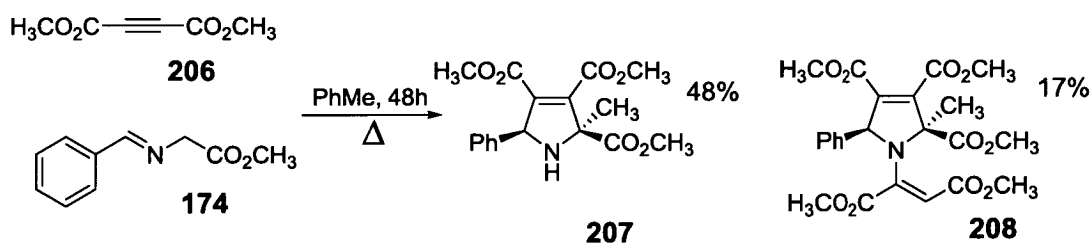
Scheme 57: Investigation of phenyl vinyl sulfonyl as a dipolarophile.

Reaction of imine **164** with phenyl vinyl sulfone and lithium bromide in refluxing THF for 20h led to the isolation of cycloadduct **205** in 53% yield. Formation of the cycloadduct **205** was again shown by the doublet of the C5 methine proton adjacent to the aromatic ring at δ 4.67 ppm; however for this derivative, a coupling constant of 8.3 Hz was obtained. The large difference in the coupling constant for the C5 methine proton of **204** and **205** means the stereochemical assignment of the compounds is tentative, as the *endo* cycloadduct would be expected given our earlier work and Tsuge and Grigg's reported results. However, Carretero reported a 5.4 Hz coupling constant between the C4 and C5 protons of **201**, suggesting that **204** may feature a *trans* stereochemical arrangement between the protons of the C4 and C5 carbons.¹⁴³

The reaction of **163** or **164** with phenyl vinyl sulfone and lithium bromide at room temperature without triethylamine unsurprisingly led to no cycloaddition occurring.

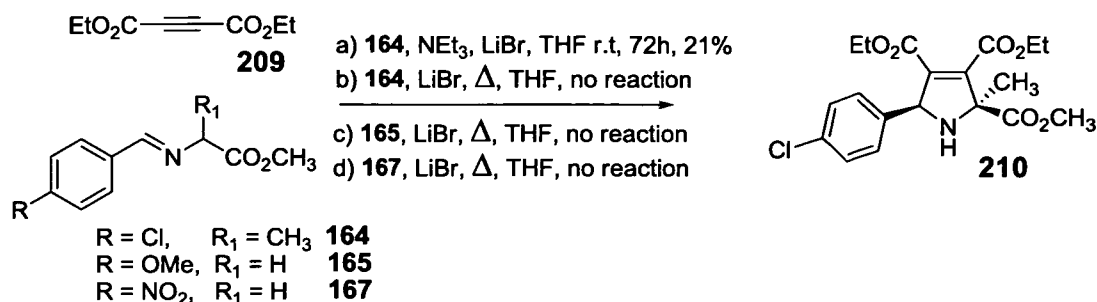
2.4.5.3 Acetylenes

The synthesis of 3-pyrrolines through azomethine ylide cycloaddition to an acetylene has been reported for a number of different methods of ylide generation,^{144,145,146} however there have been few reports from stabilised azomethine ylides. Grigg reported the cycloaddition of acetylenic dipolarophiles to arylidene imines to yield the corresponding 3-pyrrolines.¹⁴⁷ These cycloadditions were performed by prototropic shift to form the ylide, and not with Grigg's more common *N*-metallated conditions. The major deficiency in these cycloadditions reported by Grigg is the competing conjugate addition of the product 3-pyrroline **207** to excess or unreacted acetylene yielding *N*-substituted Michael adduct **208**, (Scheme 58). Grigg also noted that 3-pyrrolines with protons in both the C2 and C5 position were unstable and prone to rapid auto-oxidation to give the corresponding pyrrole derivatives.



Scheme 58: Grigg's cycloaddition of imine **174** to dimethyl acetylenedicarboxylate **206**.¹⁴⁷

Thus the cycloaddition of a variety of imines and diethyl acetylenedicarboxylate **209** was investigated, (Scheme 59).



Scheme 59: Investigation of acetylenedicarboxylate as a dipolarophile.

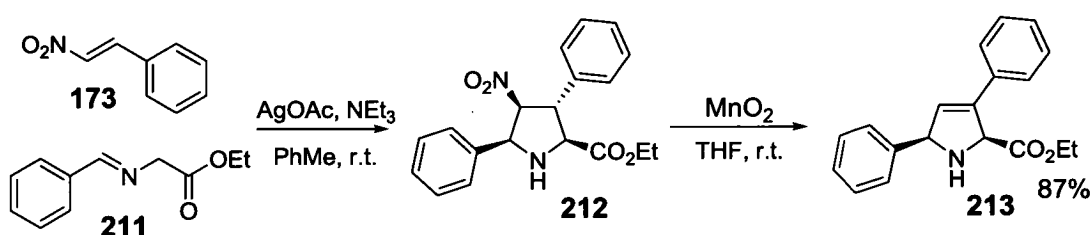
Cycloaddition was only observed with Tsuge's original conditions (Scheme 59, a), yielding pyrrolidine **210** from imine **164** derived from alanine and 4-chlorobenzaldehyde. Whilst analysis of the ^1H NMR spectrum of the crude reaction mixture appeared to show a high conversion of the imine to cycloadduct, a 21% yield of **210** was isolated after chromatography. This indicated possible decomposition of the product, although auto-oxidation is not possible for this derivative. Structural assignment of **210** was confirmed through analysis of the ^1H NMR spectrum with the C5 methine proton resonating as a singlet at δ 4.59 ppm due to the product now being a pyrroline.

All attempts to perform cycloaddition at increased temperature without triethylamine led to complicated product mixtures by ^1H NMR, with no resonances at approximately δ 4.6 ppm indicating pyrroline formation. It is not clear if the cycloadducts formed and decomposed under the reaction conditions, as it was observed that the 3-pyrroline products are less stable than the corresponding pyrrolidines.

2.4.5.4 Acetylene equivalents

Given the low yield of product obtained from the azomethine ylide cycloaddition to diethyl acetylenedicarboxylate (**167**), which required base to achieve cycloaddition, research turned to possible acetylene equivalents. Nyerges reported an interesting reaction of 3-nitropyrrolidines such as **212**, [formed from an azomethine cycloaddition reaction of 2-nitrostyrene (**173**) and imine **211**], with manganese dioxide to yield 3-pyrrolines such as **213**, (Scheme 60).¹⁴⁸ This is the only reported transformation of this type on nitro-styrene

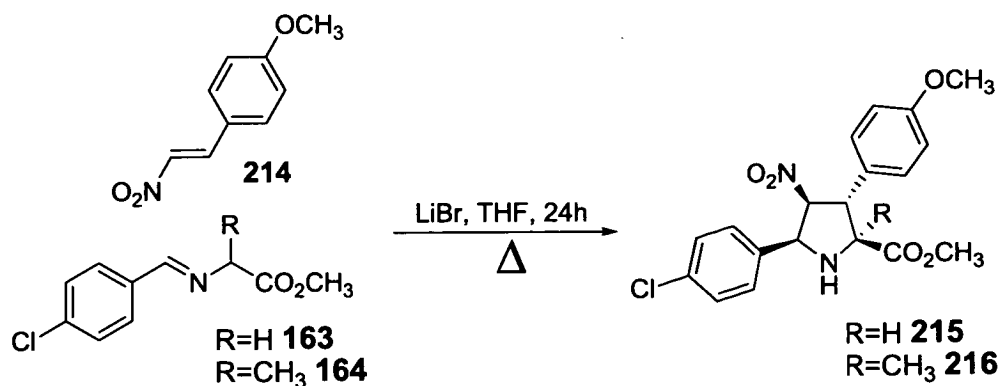
derived cycloadducts **212**, despite the popularity of **173** as a dipolarophile in azomethine cycloaddition reactions. Nyerges' report demonstrates the use of nitrostyrene as a substituted acetylene equivalent, and he has also reported methods for the *in situ* generation of unstable nitroethylene and utility in azomethine cycloaddition reactions.¹⁴⁹ Given Nyerges has not reported the manganese dioxide mediated elimination on a nitroethylene cycloadduct, it remains to be seen whether such an elimination would be disfavoured without the β -aromatic ring. We suggest that nitroethylene is unlikely to show utility as an unsubstituted acetylene equivalent.



Scheme 60: Nyerges MnO_2 mediated nitro-pyrrolidine to pyrroline conversion.¹⁴⁸

Despite the many reports on the use of nitrostyrenes as dipolarophiles, surprisingly it is only Grigg, who mainly uses silver, who has reported the use of a lithium bromide and base catalysed cycloaddition with this class of dipolarophile.¹⁵⁰ Cossio has reported computational studies on the cycloaddition of this class of dipolarophile to ylides formed *via* prototropic shift of an imine,¹³⁵ as well as studies on microwave assisted cycloadditions of nitrostyrenes.¹³⁴

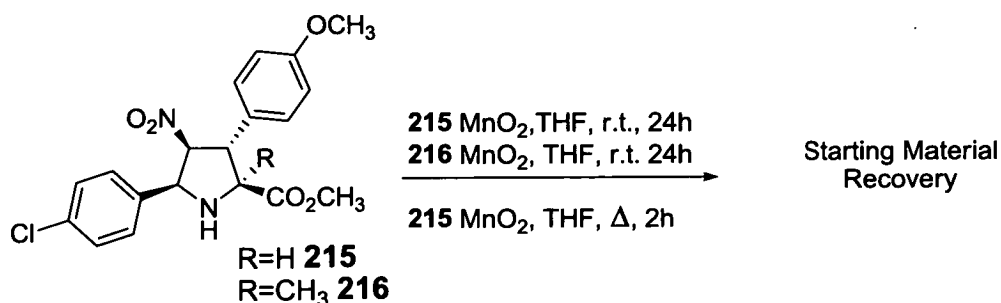
Reaction between imines **163** and **164** under our modified conditions with the *para*-methoxy derivative of 2-nitrostyrene **214** were successful with the glycine derived imine **163** giving a 64% yield of cycloadduct **215**, and alanine derived imine **164** giving a quantitative yield of cycloadduct **216**, both as a single diastereomers, (Scheme 61).



Scheme 61: Nitrostyrene azomethine ylide cycloaddition reactions under our modified conditions.

Comparison of the ¹H NMR spectra of the cycloaddition products to the NMR data reported by Nyerges for the diphenyl pyrrolidine **212** was consistent with the formation of **215** and **216**. The diagnostic doublet of the C5 methine proton of **215** resonated at δ 4.91 ppm, and the methine proton of the C4 carbon adjacent to the nitro group was also diagnostic, being a doublet of doublets at δ 5.22 ppm. The coupling constants between each proton, J_{C4-C5} = 6.6 Hz, J_{C3-C4} = 3.6 Hz, are consistent with those reported by Nyerges.¹⁴⁸ The ¹H NMR of **216** was analogous to **215**, however it featured a singlet resonance for the C2 methyl group at δ 1.20 ppm.

Attempts to reproduce Nyerges' manganese dioxide facilitated elimination on our pyrrolidine adducts **215** and **216** were unfortunately unsuccessful. This was despite using several sources of manganese dioxide, including freshly prepared material, (Scheme 62).¹⁵¹



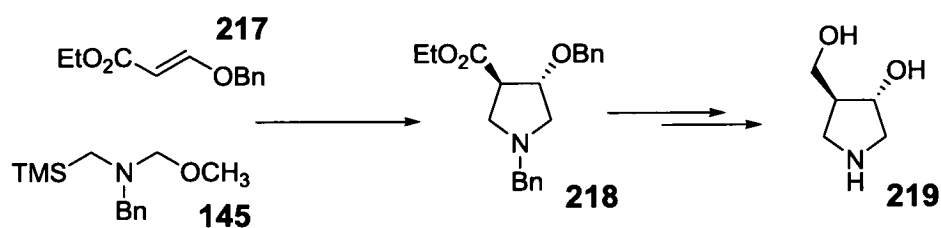
Scheme 62: Attempted elimination of nitro-pyrrolidines **192** and **193** to their pyrroline derivatives.

In each case it was clear that no elimination had taken place as the NMR revealed starting material remained, highlighted by the resonance of the proton geminal to the nitro group at δ 5.6 ppm for **216**, and δ 5.2 ppm for **215**.

Whether a base catalysed elimination with sodium hydroxide in methanol could perform this elimination was also investigated. Unfortunately, this was unsuccessful, and again there was no evidence of a change in the NMR spectrum obtained.

2.4.5.5 (*E*)-Methyl 3-(benzyloxy)acrylate

Given the difficulty of obtaining cycloaddition with the acetylenes, we looked to (*E*)-ethyl 3-(benzyloxy)acrylate **217** a dipolarophile that had been utilised by Tyler, which is formed by the conjugate addition of benzyl alcohol to ethyl propiolate.¹⁵² Tyler performed an azomethine cycloaddition with the ylide generated by desilylation of *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine **145** in a patented synthesis of amino-diol **219** that he had previously utilised as an intermediate in the synthesis of potent purine nucleoside phosphorylase inhibitors, (Scheme 57).¹⁵³



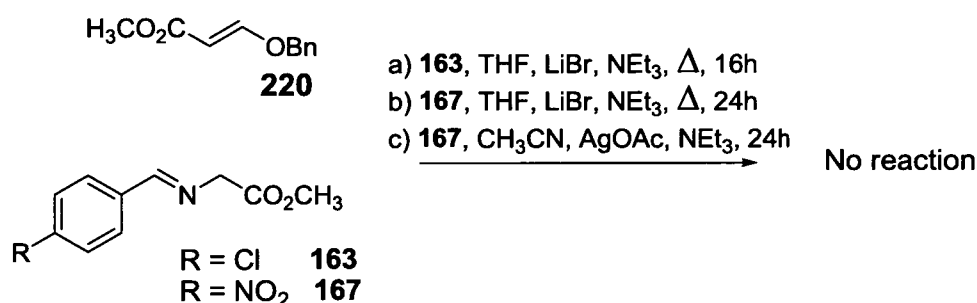
Scheme 63: Tyler's patented synthesis of pyrrolidine diol **219**.¹⁵²

As a dipolarophile that would directly introduce a protected hydroxyl functionality into the pyrrolidine ring, it should be more reactive than vinylene carbonate due to the electron withdrawing ester substituent, however at the same time the protected alcohol does increase the electron density of the alkene.

The methyl analogue of **217** was prepared for simplicity of NMR analysis, and was synthesised by treating methyl propiolate with benzyl alcohol in the presence of an equivalent of triethylamine as base. Purification by chromatography led to the synthesis of

the dipolarophile **220** in 57% yield. ^1H NMR analysis confirmed that only the *trans* isomer was formed, with the two alkene resonances at δ 5.32 and 7.68 ppm having a reciprocal coupling constant of 12.6 Hz.

Thus investigation into cycloaddition under our improved Tsuge conditions was commenced, (Scheme 58).



Scheme 64: Attempted utilisation of benzyloxy dipolarophile **220**.

Due to the deactivated nature of dipolarophile **220**, initial reaction with imine **163** in refluxing THF was performed with both lithium bromide and triethylamine. ^1H NMR analysis of the crude reaction mixture gave no evidence of cycloaddition formation, with unreacted acrylate and imine isolated. Reaction under the same conditions with the slightly more reactive imine **167** again gave no reaction. Reaction of **167** and benzyloxy acrylate **220** using silver acetate, as per Grigg's method, with triethylamine instead of DBU to promote reaction also showed no indication of cycloaddition by analysis of the crude reaction mixture by ^1H NMR. Further reaction utilising DBU and heat could be attempted, however this was not investigated.

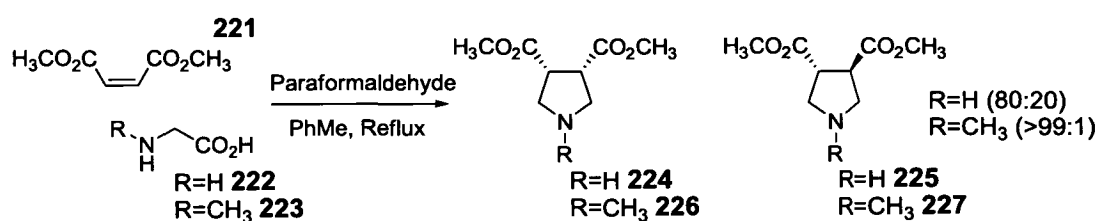
Given the difficulties with the cycloadditions with the *N*-metallated stabilised ylides, and the inherent transformations that would be required to perform syntheses of pyrrolidine alkaloids. Such as when targeting codonopsinine it would be required to perform decarboxylation of the C2/C5 ester group. It was decided to investigate the decarboxylation route to the generation of azomethine ylides, and to determine if this is a feasible method for the pyrrolidine synthesis.

2.5 Decarboxylative cycloaddition

2.5.1 Introduction to decarboxylative azomethine ylide chemistry

Given the inability of the stabilised *N*-metallated azomethine ylide chemistry to undergo cycloaddition with the less reactive, but more synthetically useful dipolarophiles such as vinylene carbonate, it was decided to investigate non-stabilised azomethine ylides generated by the decarboxylation of iminium carboxylates.

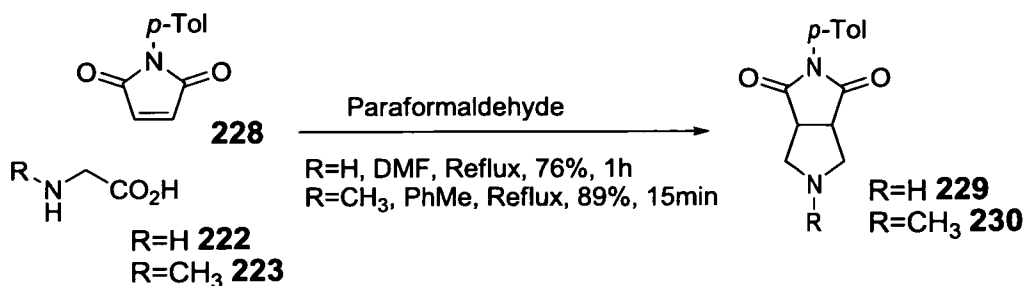
In the initial investigation into this method of azomethine ylide generation and cycloaddition, Joucla reported an interesting difference in stereochemical outcome between the use of *N*-substituted amino acids and their primary counterparts, (Scheme 65).¹⁵⁴



Scheme 65: Joucla's initial studies into decarboxylative cycloaddition.¹⁵⁴

Performing studies on the cycloaddition of the ylide formed through decarboxylation of the iminium carboxylate formed by condensation of paraformaldehyde and amino acids with diethyl maleate **221**, an interesting observation was noted. When using sarcosine (**223**, *N*-methylglycine), no epimerisation / isomerisation of the *cis*-related esters was observed, and **226** was the only isolated cycloadduct. However, when glycine (**222**) was used, two diastereomers, **224** and **225**, were observed. The cause of this was not determined, as it could have been isomerisation of the maleate to fumarate prior to cycloaddition, or self catalysed base epimerisation of the pyrrolidine product to the more stable *trans* isomer. Interestingly, Joucla reported the yields of cycloadducts were similar for both amino acids. This contradicts a report from Tsuge, which discussed the reactivity difference between

primary and secondary amino acids under decarboxylative conditions, and found that the reactivity of the ylides derived from secondary amino acids to be higher, (Scheme 66).¹⁴²



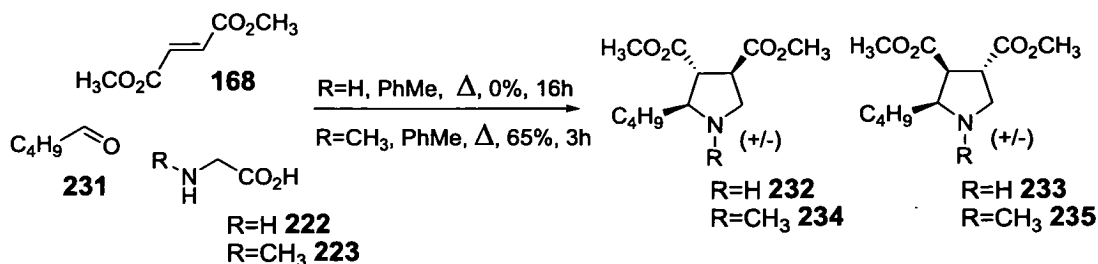
Scheme 66: Tsuge's investigation of decarboxylative cycloaddition.¹⁴²

In studies with *N*-tolylmaleimide (**228**), the glycine derived cycloadduct **229** required a far longer reaction time in solvent of a much higher boiling point than the sarcosine derived product **230** (153°C vs. 111°C, DMF:PhMe).¹⁴² This reactivity difference is most likely caused by a higher temperature required to perform the decarboxylation to form the ylide in the glycine case, (Scheme 31).

Tsuge has also demonstrated the large variety of carbonyl sources that can be utilised in these decarboxylative cycloadditions, such as paraformaldehyde, benzaldehydes and simple aliphatic aldehydes such as ethanal and propanal, as well as ketones such as acetone and cyclohexanone.^{142,155} The use of a long chain aldehyde would be required to target preussin (**118**), which features a long alkyl chain at the C5 position of the pyrrolidine ring.

2.5.2 Initial investigation into decarboxylative azomethine chemistry

To independently confirm the difference in reactivity between primary and secondary amino acids towards decarboxylative azomethine ylide cycloaddition, valeraldehyde **231** and dimethyl fumarate (**168**) were reacted with sarcosine, and with glycine in refluxing toluene, (Scheme 67).



Scheme 67: Initial reactivity test of *N*-substituted amino acids.

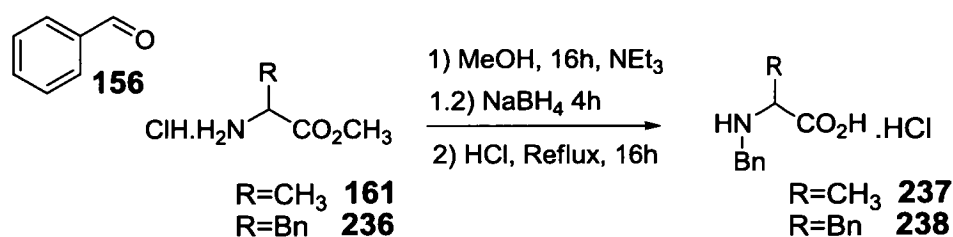
Reaction with sarcosine **223** gave a mixture of cycloadducts, proposed to be the *exo* and *endo* adducts **234/235** in 65% yield. The mixture was determined as two diastereomers, in an approximately 3:2 ratio from the integration of the two *N*-methyl resonances at δ 2.23 and δ 2.27 ppm in the ^1H NMR. Stereochemical assignment of the cycloadducts was not possible due to overlap of the remaining proton resonances, however the ^{13}C NMR spectrum showed 26 resonances consistent with the formation of two diastereomers. This stereochemical assignment was proposed given that no base (other than the product pyrrolidines) was present in the reaction, therefore epimerisation of the cycloadducts was unlikely, although this possibility cannot be ruled out completely.

The corresponding reaction with glycine **222**, when analysed by ^1H NMR spectroscopy, failed to show any evidence of cycloaddition under the same conditions, with the only identifiable compound isolated being unreacted dimethyl fumarate. This change in reactivity between primary and secondary amino acids is in correlation with the results reported by Tsuge.¹⁴²

Given the success of the cycloaddition with sarcosine, the aldehyde and amino acid ylide precursors were investigated to determine whether the C2 and C5 functionalities of preussin and codonopsinine could be introduced. For codonopsinine, the C5 methyl group could come from alanine, whilst the C2 aromatic ring could come from anisaldehyde. With preussin, phenylalanine could be utilised to introduce the C2 benzyl group, and decanal for the C5 alkyl chain.

Given the higher reactivity of secondary amino acids towards cycloaddition, the *N*-benzyl amino acids were utilised as starting materials as *N*-methyl alanine and *N*-methyl phenylalanine are not readily available. The benzyl group can also be cleaved through hydrogenation, allowing methylation after formation of the pyrrolidine ring. Tsuge also reported little difference in the reactivity of the cycloaddition of *N*-benzyl glycine *versus* *N*-methyl glycine in decarboxylative cycloadditions with ethanal and maleimide.¹⁵⁵

The *N*-benzyl amino acids were obtained as per literature methods.¹⁵⁵ Condensation between benzaldehyde and amino esters **161** and **236**, followed by reduction with sodium borohydride gave the *N*-benzyl esters in quantitative yield. Acid hydrolysis then produced the amino acid hydrochlorides in quantitative yield, (Scheme 68).

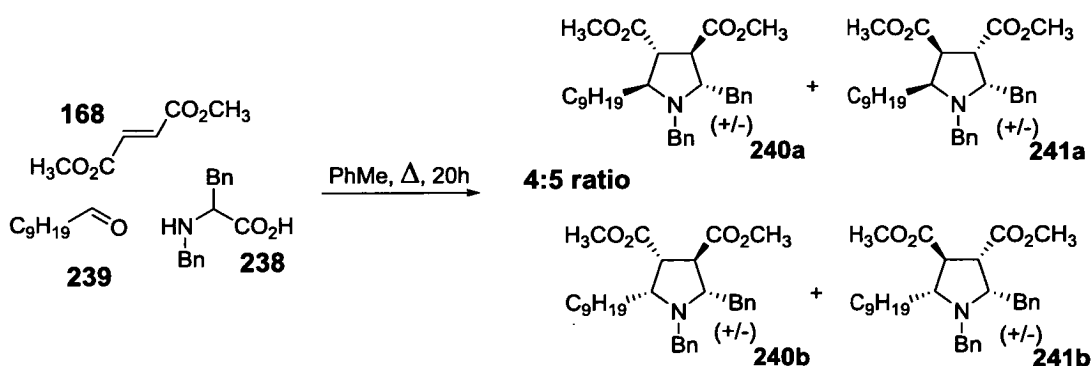


Scheme 68: Synthesis of *N*-benzyl amino acid hydrochlorides.

Formation of the *N*-benzyl derivatives was confirmed by comparison of the ¹H and ¹³C NMR spectra to the literature.¹⁵⁶ Key resonances in the ¹H NMR spectrum were the appearance of the diastereotopic *N*-benzyl methylene protons, present as doublets at δ 3.37 and δ 3.53 ppm for alanine, and δ 3.30 and δ 3.48 ppm for phenylalanine, with geminal coupling constants 12.5 Hz and 12.6 Hz respectively. Introduction of five more carbon resonances in each ¹³C NMR spectrum was further evidence of *N*-benzylation.

Prior to cycloaddition, the free *N*-benzylamino acids were liberated from the *N*-benzylamino acid hydrochlorides by neutralising with an equivalent of sodium hydroxide or potassium hydroxide in water, then concentrating the solution to dryness to give a mixture of the amino acid and sodium or potassium chloride.

Cycloaddition between dimethyl fumarate (**168**), *N*-benzyl phenylalanine (**238**) and decanal (**239**) in a three component coupling reaction to approach the preussin pyrrolidine core gave a 4:5 ratio of two inseparable diastereomers, **240** and **241**, in 33% yield, (Scheme 69).



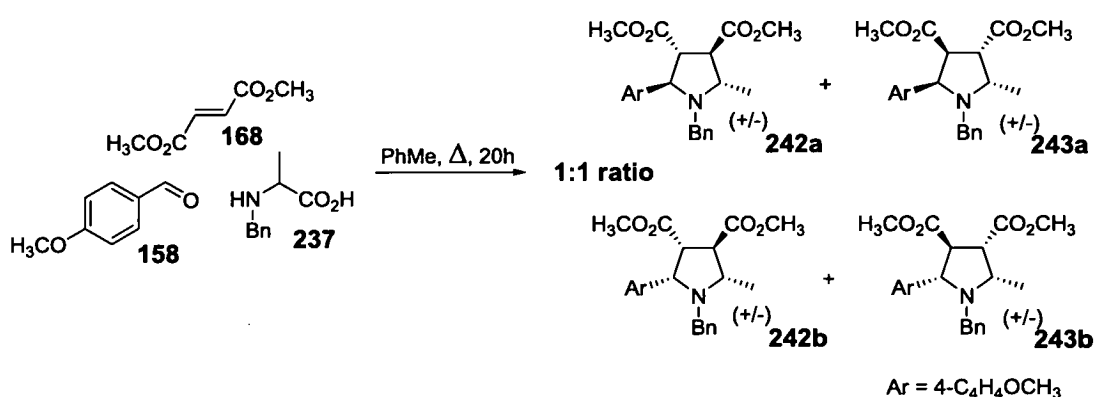
Scheme 69: Approach to a preussin pyrrolidine core.

Analysis of the ^1H NMR spectra of the products showed two diastereomers **240** and **241**, particularly evident by the presence of four methyl ester resonances at δ 3.29, 3.50, 3.69 and 3.72 ppm. The ratio of diastereomers was determined by the doublet of doublets for one of the diastereotopic protons of the methylene of the C2 benzyl group at δ 2.89 and 2.99 ppm, and was supported by the methyl ester resonances.

The formation of two diastereomers was surprising in regard to the 3:2 mixture of *exo/endo* cycloadducts obtained from cycloaddition between valeraldehyde, sarcosine and dimethyl fumarate, (Scheme 67). Reaction with *N*-benzylphenylalanine introduces another stereogenic centre to the product pyrrolidine, and therefore it might be expected that four diastereomers would be obtained. Overlap of the methine pyrrolidine ring resonances in the ^1H NMR spectrum did not allow stereochemical assignments to be performed. As such, given that the *exo* and *endo* adducts were obtained from valeraldehyde and sarcosine, it is tentatively proposed that they were observed again, and that selective reaction of either the *syn* or *anti* form of the ylide occurred to give either **240a** / **241a** or **240b** / **241b**. However the formation of **240a** / **241a** is more likely given results disclosed later, *vide supra*.

Due to the low yield obtained, for future cycloaddition attempts the dipolarophile was kept as a limiting reagent and excess ylide forming reagents were added.

Three component coupling between anisaldehyde (**158**), *N*-benzyl alanine (**237**) and dimethyl fumarate (**168**) gave an inseparable, approximately 1:1 mixture of diastereomers **242** / **243** in 97% yield, which again did not allow stereochemical assignment, (Scheme 70).



Scheme 70: Approach to a codonopsinine pyrrolidine core.

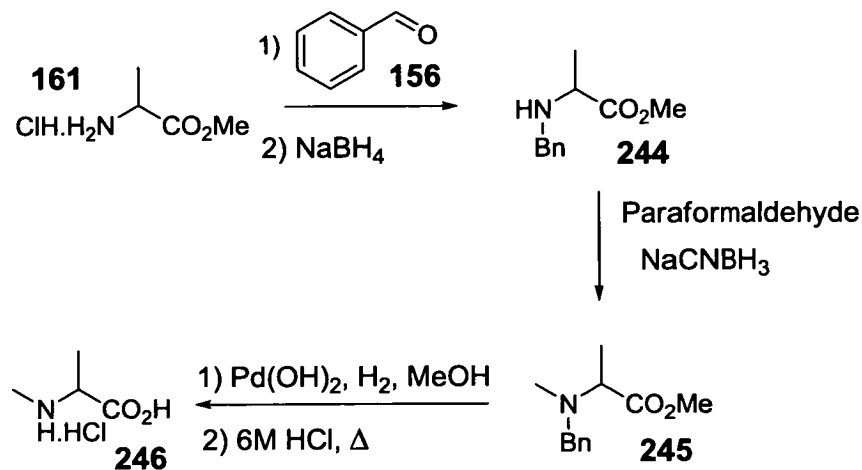
Doublet resonances in an \approx 1:1 ratio at δ 1.11 and 0.90 ppm in the ^1H NMR spectrum were diagnostic for the C5 methyl groups of **242** and **243**. Four methyl ester or methoxy resonances were visible, at δ 3.14, 3.72, 3.77 and 3.87 ppm with two resonances overlapped at δ 3.64 ppm. Coupling constants of the methine protons of each diastereomer at C1 adjacent the aromatic ring resonating at δ 4.11 and 4.07 ppm were visible with $J = 7.0$ Hz in both cases, suggesting that the C1 and C2 groups had the same orientation in each diastereomer, and as such the stereochemical assignment given is highly tentative.

Given the success of the formation of the *N*-benzyl cycloadducts to form the pyrrolidine core with the desired substituents at C2 and C5, the *N*-methyl amino acids were investigated as both codonopsinine and preussin feature an *N*-methyl functionality.

2.5.3 New synthetic method for the synthesis of *N*-methyl primary amino acids

Synthesis of *N*-methyl amino acids is not trivial and much research has been devoted to this task. Unlike *N*-benzylation, *N*-methylation of primary amino acids is a far more complex process, as the equilibrium for the reaction with formaldehyde to give the methyleneamino derivative does not favour the products. If the imine is reduced to the *N*-methyl *in situ* with sodium cyanoborohydride then an inseparable mixture of *N*-methyl and *N*-dimethyl is obtained.¹⁵⁷ The most popular methods involve selective *N*-benzylation followed by *N*-methylation, then debenylation.^{158,156,159} Typically this is performed by forming a Schiff-base by condensation of the amino acid or ester with benzaldehyde, followed by reduction of the benzylidene with borohydride to give the *N*-benzyl amino acid/ester. The *N*-benzyl amino acid/ester is then treated with formaldehyde/formic acid forming the imine, which can be reduced *in situ* to the *N*-benzyl-*N*-methyl amino acid/ester with sodium cyanoborohydride. Debenzylation by hydrogenation yields the desired *N*-methyl amino acid/ester.

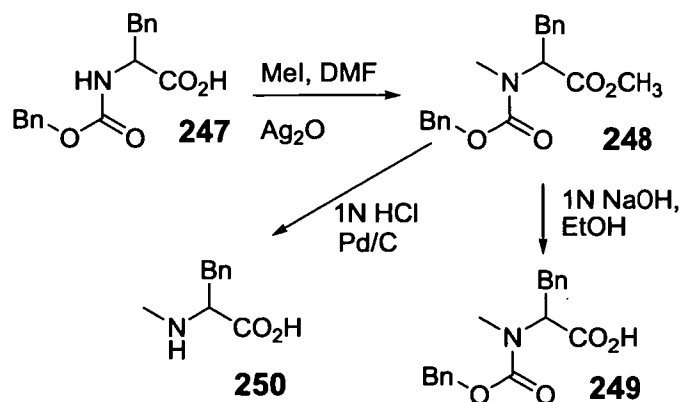
Following this synthetic protocol for the synthesis of *N*-methyl alanine from the methyl ester hydrochloride of alanine, it was discovered that whilst yields were generally good, a challenging chromatographic separation was required after alkylation, and the debenylation was difficult to reproduce, requiring Pd(OH)₂ as catalyst, rather than just palladium on carbon, (Scheme 71).



Scheme 71: Synthesis of *N*-methylalanine.

Formation of *N*-benzylalanine methyl ester **244** was identified by the appearance of the aromatic resonances in the ^1H NMR spectrum between δ 7.23 – 7.38 ppm. Conversion to the *N*-benzyl-*N*-methyl derivative **245** was shown by the appearance of the *N*-methyl resonance at δ 2.29 ppm. Debenzylation under hydrogenation conditions gave the secondary amine, which underwent hydrolysis of the ester in 6M HCl, and after concentration led to the formation of **246**, the hydrochloride salt of *N*-methyl alanine. Successful synthesis was shown by the disappearance of the methyl ester resonance at δ 3.73 ppm in the ^1H NMR spectrum, and by the lack of aromatic resonances visible in either the ^1H or ^{13}C NMR spectra. Whilst this synthesis of the *N*-methyl amino acid was successful, the slow hydrogenation step often led to incomplete debenzylation, and the requirement for the use of chromatography after alkylation was not desirable for such a fundamental synthesis.

Therefore we developed an alternative approach based on a report by Olsen.¹⁶⁰ Olsen reported the *N*-methylation of *N*-benzyloxycarbonyl and *N*-*t*-butoxycarbonyl protected amino acids. This involves alkylation of the acid functionality of the amino acid as well as the nitrogen, however he was able to saponify the ester to yield the *N*-methyl-*N*-protected amino acids, or perform an acidic hydrolysis to yield the *N*-methyl amino acids, (Scheme 72).

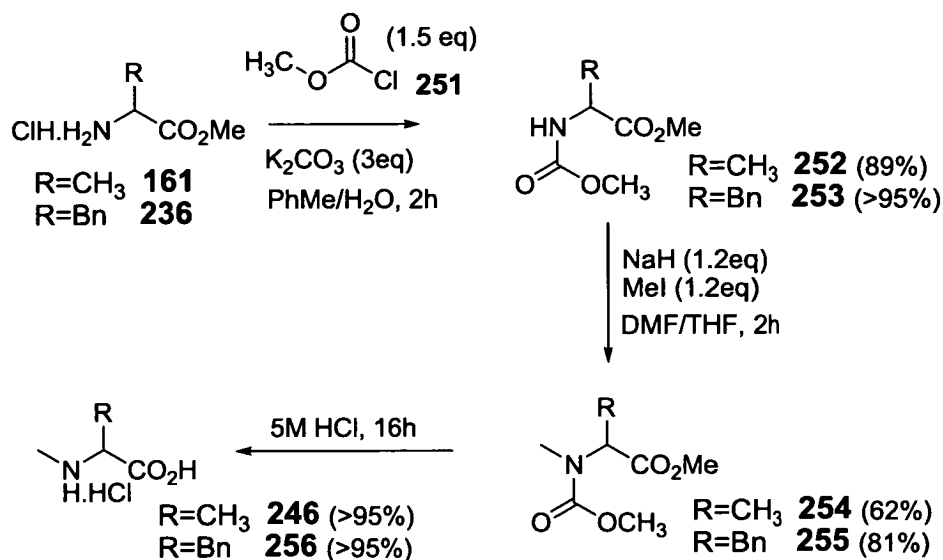


Scheme 72: Olsen's synthesis of *N*-methyl amino acids.¹⁶⁰

Whilst Olsen's method is effective, we proposed some alternative conditions. Starting with the methyl ester would limit the required amount of iodomethane to perform the methylation, and in recent reports such as that by Mlynarski,¹⁶¹ in which he was targeting *N,N*-dialkyl amino acids, the alkylation of *N*-benzyloxycarbonyl amino acids is performed with sodium hydride and iodomethane, thus removing the need for silver salts.

A recent report from Jain showed that removal of benzyloxycarbonyl and methyl ester functionalities could be performed using hydrolysis with strong acid (6N HCl) at elevated temperatures (100°C), eliminating the need to perform a hydrogenolysis.¹⁶²

Thus, a test reaction to make *N*-methyl alanine was performed. Using Hutton's method for benzyloxycarboxylation, the methyl ester of alanine was converted to its benzyl carbamate by treatment with benzyl chloroformate.¹⁶³ The carbamate was then deprotonated with sodium hydride, and simple $\text{S}_{\text{N}}2$ reaction with iodomethane yielded the *N*-methyl-*N*-benzyloxycarbonyl derivative. Hydrolysis of the carbamate and ester functionalities was then achieved by reflux in 5M hydrochloric acid overnight, yielding *N*-methylalanine hydrochloride. While this method was successful, the poor atom-efficiency due to use of benzyl chloroformate was not desirable, therefore the much cheaper methyl chloroformate **251** was used in subsequent reactions, although CBZ would be useful for the selective deprotection to the amino ester, (Scheme 73).



Scheme 73: Synthesis of *N*-methyl amino acids.

The methyl ester hydrochlorides of alanine and phenyl alanine were treated with methyl chloroformate and potassium carbonate in a two phase toluene/water solvent system. Formation of the carbamate derivative **252** was observed in the ¹H NMR spectrum by the introduction of the carbamate methyl group at δ 3.60 ppm. Formation of **253** was observed by the introduction of two rotameric resonances at δ 3.63 and 3.64 ppm for the *N*-methoxycarbonyl group, and two methyl ester resonances at δ 3.69 and 3.70 ppm. *N*-Methylation of **252** and **253** was achieved by reaction with sodium hydride and iodomethane in DMF/THF to give the *N*-methyl-*N*-methoxycarbonyl derivatives **254** and **255**, respectively. *N*-Methylation was confirmed for **254** through introduction of rotameric *N*-methyl resonances at δ 2.35 and δ 2.38 ppm in the ¹H NMR spectrum. Analogously *N*-methyl resonances at δ 2.75 and δ 2.81 ppm were also visible in the ¹H NMR of **255**. *N*-Methyl amino acid hydrochlorides **246** and **256** were isolated by hydrolysis of **254** and **255** with 5M HCl at reflux overnight. Formation of the secondary amino acids was shown by loss of the methyl ester and *N*-methoxycarbonyl resonances at approximately δ 3.6 ppm in the ¹H NMR spectra of **254** and **255**.

Thus we have refined the process for the synthesis of *N*-methyl amino acids, giving a three step process starting from amino esters, without the need for chromatography. Using this

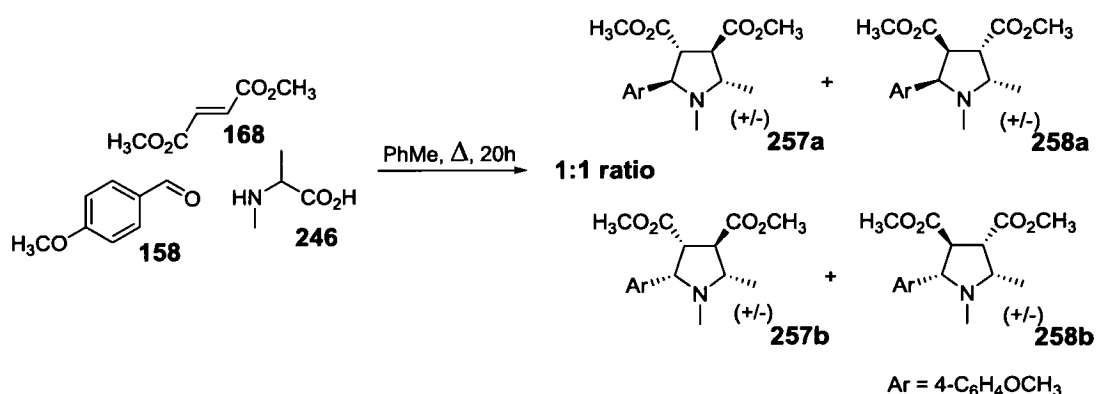
method *N*-methylphenylalanine hydrochloride was synthesised in 81% yield over three steps.

It is important to note that whilst we desired the *N*-methyl amino acids, and as such hydrolysed both the ester and the carbamate in one step, selective hydrolysis of the carbamate over the ester can be achieved by hydrolysis with HBr in glacial acetic acid at room temperature, allowing access to the *N*-methyl amino esters.^{164, 165}

2.5.4 Synthesis of *N*-methyl pyrrolidine alkaloid core from *N*-methyl amino acids

Repeating the three component couplings performed earlier with *N*-benzyl amino acids with the newly synthesised *N*-methylamino acids gave the core structures of our target natural products with three substituents of the alkaloids in place.

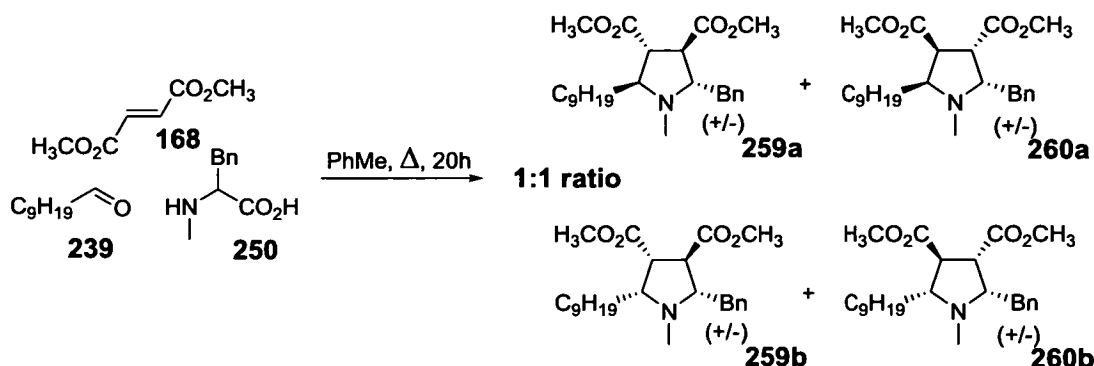
Reaction of *N*-methylalanine, anisaldehyde and dimethyl fumarate led to the synthesis of an inseparable 1:1 mixture of two diastereomers, **257** and **258**, in 94% yield, (Scheme 74).



Scheme 74: Synthesis of *N*-methyl codonopsinine core.

As with the previous *N*-benzyl reaction stereochemical assignment was not possible due to overlapped resonances in the ¹H NMR spectrum. Comparison with the previous spectroscopic data for *N*-benzyl pyrrolidines **242** and **243** confirmed formation of the **257** and **258**, with two doublets at δ 1.16 and δ 0.91 ppm, corresponding to the methyl group at the C5 position of the each diastereomer. The *N*-methyl resonance of each diastereomer was also distinguishable at δ 2.11 and δ 1.98 ppm respectively.

Cycloaddition between decanal, *N*-methylphenylalanine and dimethyl fumarate gave an inseparable 1:1 mixture of two diastereomers in 56% yield, (Scheme 75).



Scheme 75: Synthesis of *N*-methyl preussin core.

As with the previous *N*-benzyl reaction, stereochemical assignment was not possible due to overlapped resonances in the ^1H NMR spectrum. Formation of pyrrolidines **259** and **260** was confirmed by comparison to the ^1H NMR obtained for the *N*-benzyl diastereomers **240** and **241**. Integration of the aromatic resonances was lowered, and this was complemented by the introduction of the *N*-methyl resonances at δ 2.37 and δ 2.31 ppm. An accurate measure of the diastereoselectivity was not possible through ^1H NMR analysis as the *N*-methyl resonances were overlapped with other signals, but indicated an approximately 1:1 ratio.

The lower yield of this cycloaddition, compared to that of anisaldehyde and *N*-methyl alanine, indicates that formation of the imine from an aliphatic aldehyde and its subsequent decarboxylation is not as efficient, or degradation processes are taking place.

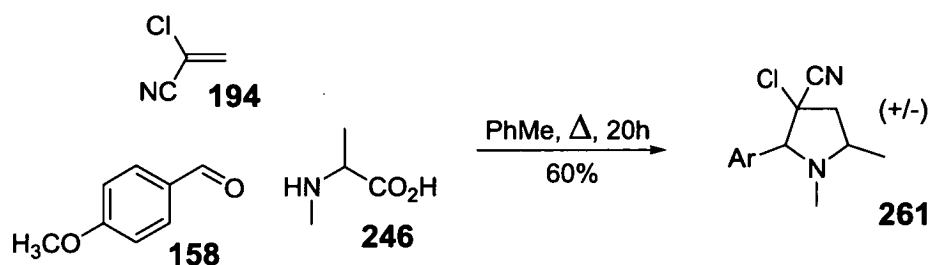
Thus, as we had developed chemistry that could introduce the 1-, 2- and 5- substituents of both pyrrolidine alkaloids, preussin and codonopsinine, through decarboxylative azomethine chemistry, development of dipolarophiles to introduce the necessary oxygenated functionalities into the 3 and 4 positions was investigated.

2.5.5 Decarboxylative cycloaddition dipolarophile investigation.

In Tsuge's initial studies into decarboxylative azomethine ylide generation, he reported trapping the ylides generated from paraformaldehyde and sarcosine or glycine by a range of dipolarophiles, including the deactivated electron rich alkene styrene, as well as phenyl vinyl sulfone, acrylates and α,β -unsaturated ketones.¹⁴² Therefore, we decided to test the scope of the reactivity of the azomethine ylide generated from anisaldehyde and *N*-methyl alanine, targeting the pyrrolidine core of codonopsinine towards a range of dipolarophiles with potential to introduce oxygenation at C3 and C4 of the pyrrolidine.

Initial studies investigated ketene equivalents α -chloroacrylonitrile and phenyl vinyl sulfone for reactivity towards cycloaddition to the non-stabilised azomethine ylide.

Reaction between anisaldehyde, *N*-methyl alanine and α -chloroacrylonitrile in refluxing toluene gave a 60% yield of three diastereomeric pyrrolidines **261**. Due to the volatility and instability of the acrylonitrile, 4.5 equivalents were utilised, added in three portions, (Scheme 76).



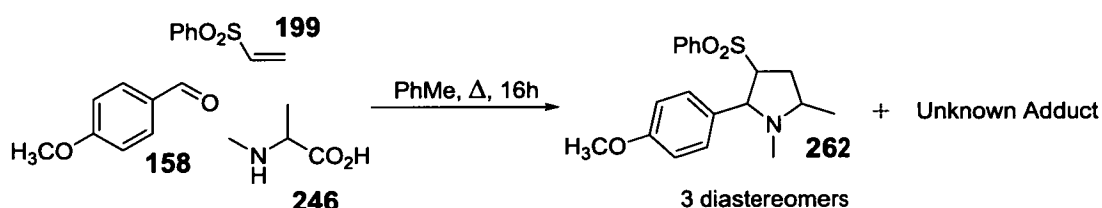
Scheme 76: α -Chloroacrylonitrile as dipolarophile.

^1H NMR spectral analysis showed three diastereomers were formed, in a 1: 0.8: 1 ratio, with diagnostic resonances for the 5-methyl group of each diastereomer, which were visible as doublets at δ 1.34, 1.27 and 1.20 ppm. Also evident were three methoxy resonances at δ 3.83, 3.82 and 3.80 ppm. Given the overlap of diagnostic resonances in the ^1H NMR spectrum, stereochemical assignment of each diastereomer was not possible. High

resolution mass spectroscopy provided evidence of pyrrolidine formation, giving a mass to charge ratio of 264.10290, $C_{14}H_{17}ClN_2O^+$ requires 264.10294.

Attempted hydrolysis of **261** to yield the corresponding 3-keto pyrrolidine through reaction with either potassium carbonate or hydrochloric acid was unsuccessful, leading in both cases to re-isolated starting material. As previously mentioned, functionalisation of the pyrrolidine amine to a carbamate would represent a potential future route into investigation towards achieving this hydrolysis.

Three component coupling between anisaldehyde, *N*-methyl alanine and phenyl vinyl sulfone led to a complex mixture of products, (Scheme 77).



Scheme 77: Phenyl vinyl sulfone as dipolarophile.

After flash chromatography, GC/MS analysis revealed a mixture of three diastereomeric cycloadducts **262** which were inseparable from an unknown decomposition product which represented the major component of the mixture. 1H NMR analysis indicated the unknown product appeared to incorporate a single anisaldehyde unit, with diagnostic doublet resonances at δ 6.78 and δ 7.05 ppm, integrating for two protons each, and two phenyl sulfonyl groups indicated by multiplet resonances between δ 7.50 - 7.68 ppm and δ 7.82 - 7.91 ppm, integrating for six and four protons respectively. Due to overlap of resonances with the three diastereomeric pyrrolidines **262**, this analysis is very tentative. GC/MS determination of the composition of the ratio of the diastereomers **262** was 1 : 1.9 : 2.4, and the ratio of the unknown product to the total combined cycloadducts was 1.5 : 1, representing an approximate yield of 40%. The GC/MS was unable to resolve a molecular ion for the unknown product, with a major fragment $m/z = 121$ likely formed by cleavage of the anisaldehyde unit.

Transformation of the phenyl sulfonyl moiety to the 3-ketopyrrolidine could be achieved as per the method reported by Craig, by treatment of **262** with *bis*(trimethylsilyl) peroxide.¹¹² However, due to the impurity of the product pyrrolidines, this was not targeted. There are also potential hazards in preparation and use of *bis*(trimethylsilyl) peroxide,¹⁶⁶ therefore other dipolarophiles were sought.

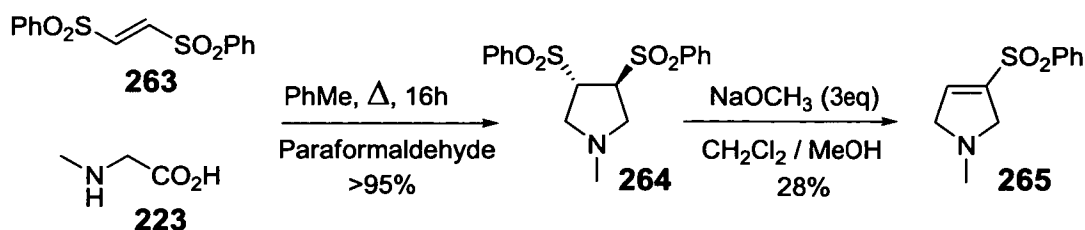
2.5.6 *trans*-1,2-Bisphenylsulfonyl ethylene as a dipolarophile

Given the predisposition of phenyl vinyl sulfone to undergo unwanted side reactions which hinder the formation of cycloadduct, attention turned to *trans*-1,2-bisphenylsulfonyl ethylene **263** as a potential route to introduce functionalisation into the 3 and 4 positions of the pyrrolidine ring. As the alkene is doubly functionalised with activating sulfonyl groups, it should be more reactive to cycloaddition compared to phenyl vinyl sulfone, therefore limiting decomposition pathways. Previously, *trans*-1,2-bisphenylsulfonyl ethylene had been reported as a dipolarophile with azomethine ylides, but only with those generated through desilylation methods.^{167,168,169} A more recent report by Carretero in the addition of the bissulfonyl ethylene to stabilised ylides reported cycloaddition followed by *in situ* phenylsulfonyl elimination to yield pyrrole adducts.¹⁷⁰

Since that first report, Carretero has subsequently reported asymmetric studies into cycloaddition of this dipolarophile using chiral phosphine catalysts and stabilised ylides to yield the corresponding pyrrolidines, which he followed by sodium amalgam mediated desulfonation of the cycloadduct to give the 3-pyrroline. In this way he has demonstrated the use of *trans*-1,2-bisphenylsulfonyl ethylene as an acetylene equivalent.¹⁷¹

Cycloaddition between this dipolarophile and an azomethine ylide generated through decarboxylation had not been previously reported, therefore an initial test reaction was performed between *trans*-1,2-bisphenylsulfonyl ethylene, sarcosine **223** and paraformaldehyde, (Scheme 78). Cycloaddition in refluxing toluene under Dean-Stark

conditions gave pyrrolidine **264** in quantitative yield. ^1H NMR spectroscopic analysis showed two doublet of doublets integrating for two protons each at δ 2.92 and δ 3.07 ppm respectively, corresponding to the non-equivalent protons adjacent to the nitrogen in the ring. HRMS also indicated product formation with a M/Z of 365.0747.



Scheme 78: *trans*-1,2-Bisphenylsulfonyl ethylene as a dipolarophile.

Padwa had reported the elimination of a phenyl sulfonyl group of the *N*-benzyl analogue of **264** with sodium methoxide to give the corresponding *N*-benzyl-3-phenylsulfonyl-3-pyrroline.¹⁷² Treatment of *N*-methyl-bissulfonyl pyrrolidine **264** with sodium methoxide led to 3-phenylsulfonyl-3-pyrroline **265** in 28% yield. Elimination and formation of 3-pyrroline **265** was confirmed by spectroscopic comparison to the *N*-benzyl derivative reported by Padwa, with key structural information provided by the presence of an alkenyl resonance in the ^1H NMR spectrum at δ 6.74 ppm.¹⁷²

Thus, a dipolarophile had been found that could turn the pyrrolidine into a pyrroline, opening up possibilities for further functionalisation. Attempted dihydroxylation of **265** using Sharpless methodology,¹⁷³ which would give an α -hydroxy ketone due to elimination of the remaining phenylsulfonyl group,¹⁷⁴ was not successful. This was not surprising as dihydroxylations of amine containing compounds are problematic.

An alternative route for dihydroxylation of **265** is through an epoxidation and ring opening method. Epoxidation of 3-pyrrolines are not widely reported, however Muraoka reported epoxidation of *N*-benzyl pyrroline **266** under a variety of acidic conditions with *m*-CPBA to give the epoxide **267**.¹⁷⁵ Muraoka's method utilised a strong acid for protonation of the tertiary amine such that *N*-oxide formation was hindered, (Scheme 79). Unfortunately we

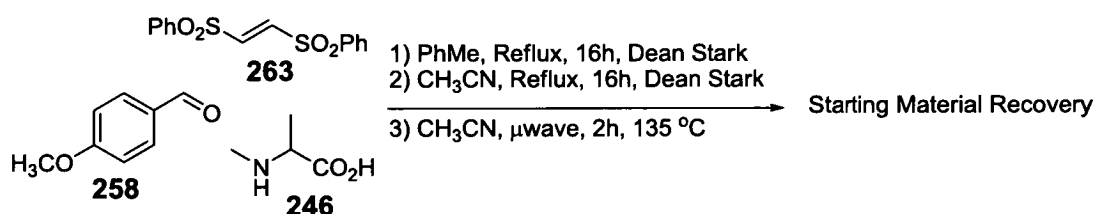
were unable to replicate this conversion to epoxidise our substituted pyrroline **265**, probably due to the alkene not being as nucleophilic due to the electron withdrawing phenylsulfonyl group.



Scheme 79: Epoxidation of *N*-benzyl pyrroline.¹⁷⁵

Before further studies into the functionalisation of pyrroline **265**, the cycloaddition between *trans*-1,2-bisphenylsulfonyl ethylene and the azomethine ylide generated from anisaldehyde and *N*-methyl alanine was investigated for application towards the synthesis of codonopsinine.

Three component coupling between anisaldehyde, *N*-methyl alanine and *trans*-1,2-bisphenylsulfonyl ethylene was unsuccessful under a variety of conditions, (Scheme 80).

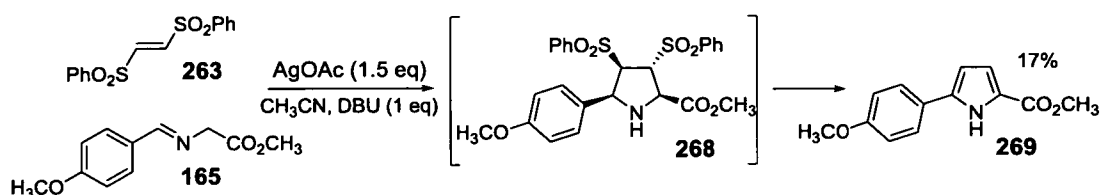


Scheme 80: Initial attempts towards codonopsine core with bis-sulfone dipolarophile.

trans-1,2-Bisphenylsulfonyl ethylene was unsuccessful in trapping the azomethine ylide formed from reaction between anisaldehyde and *N*-methyl alanine in a toluene reflux under Dean-Stark conditions. To determine if a change in the polarity of the solvent would assist cycloaddition, the reaction was attempted in an acetonitrile reflux, as well as in a sealed tube at 125°C in a microwave reactor. In both cases, analysis of the crude reaction mixture by ¹H NMR spectroscopy did not show any evidence that cycloaddition had occurred. In all reactions, unreacted dipolarophile and aldehyde were isolated. This

surprising lack of reactivity could be explored through the use of alternative aromatic aldehyde derivatives to understand the lack of reactivity in this case.

This result led us to reinvestigate stabilised azomethine ylide chemistry to approach the synthesis of codonopsinine. Cycloaddition between the imine generated from the methyl ester of glycine and anisaldehyde (**165**) and *trans*-1,2-bisphenylsulfonyl ethylene was attempted using the conditions described by Grigg, with silver acetate and DBU in acetonitrile (Scheme 81).¹⁷⁶

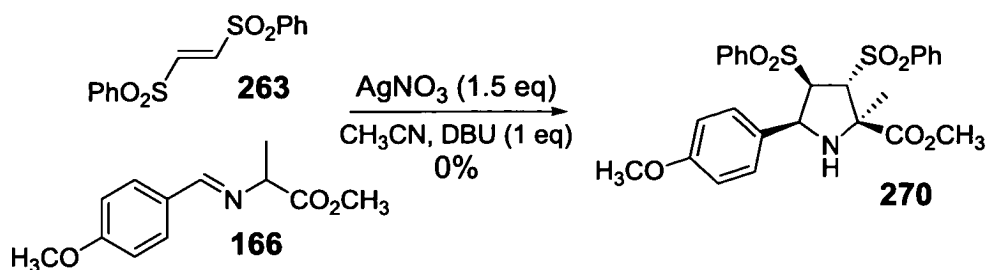


Scheme 81: *trans*-1,2-Bisphenylsulfonyl ethylene as a dipolarophile with stabilised ylide.

Purification of the product through silica gel chromatography did not yield expected cycloadduct **268**, but instead resulted in isolation of pyrrole **269**, in 17% yield. Structural identification of the pyrrole was determined by comparison of the ¹H NMR spectrum with the spectroscopic details reported by Driver.¹⁷⁷ The key spectroscopic identifier was the simplification of the aromatic resonances in the ¹H NMR spectrum, with only the two doublets of the *para*-substituted benzene ring at 7.52 and 6.93 ppm, and pyrrolic resonances as a multiplet between 6.42-6.45 ppm. The most likely cause of this elimination is a base-induced mechanism, occurring due to the use of DBU to promote the cycloaddition. Indeed Carretero had recently reported DBU-promoted elimination of the cycloadduct **268**, formed from the stabilised ylide generated from **165** undergoing cycloaddition with triethylamine and a copper/phosphine catalyst system, to give pyrrole **269**.¹⁷⁰

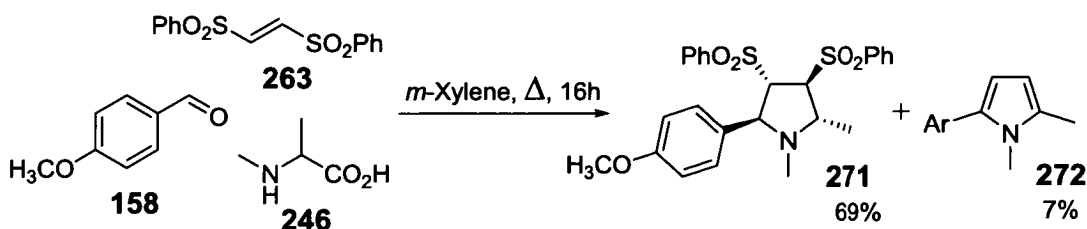
In an attempt to prevent this elimination, cycloaddition was attempted between *trans*-1,2-bisphenylsulfonyl ethylene and alanine derived imine **166**, as the product pyrrolidine would

not possess the relatively acidic β -hydrogen adjacent to the ester. Unfortunately the cycloaddition did not occur, even under the more reactive method of Grigg (Scheme 82).



Scheme 82: *trans*-1,2-Bisphenylsulfonyl with alanine derived imine **157**.

Given the difficulties encountered with elimination of the phenylsulfonyl groups of the product pyrrolidines formed through stabilised azomethine ylide chemistry using *trans*-1,2-bisphenylsulfonyl ethylene, decarboxylative ylide generation was again investigated, as no base is utilised in the ylide generation, which was believed to be driving the elimination. Given that reaction of *N*-methyl alanine and anisaldehyde generated the corresponding azomethine ylide at reflux in toluene, and this ylide was trapped by more reactive dipolarophiles, the reaction temperature was increased in an attempt to overcome the barrier to cycloaddition with *trans*-1,2-bisphenylsulfonyl ethylene. Changing solvent from toluene to *m*-xylene, which has a boiling point of 139°C, 28°C higher than toluene, led to three component coupling of *N*-methyl alanine, anisaldehyde and 1,2-*trans*-bisphenylsulfonylethylene occurring, giving a 69% yield of the desired pyrrolidine **271**, (Scheme 83).



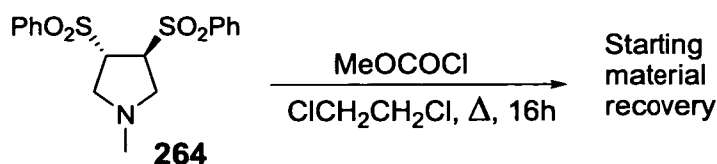
Scheme 83: *trans*-1,2-Bisphenylsulfonyl ethylene cycloaddition in refluxing xylene.

Analysis of the ^1H NMR showed cycloaddition had occurred, as evidenced by the *N*-methyl resonance at δ 2.01 ppm, as well as the diagnostic doublet of the C5 methyl group at δ 1.16 ppm, (J = 6.8 Hz). Interestingly, as confirmed by the presence of only 7 aliphatic signals in the ^{13}C NMR, only one diastereomer had been formed in the cycloaddition. This is in direct comparison to the two diastereomers formed from the dimethyl fumarate analogue, (Scheme 67). The relative stereochemistry around the ring was indeterminable by ^1H spectroscopy due to overlap of the resonances, however the all *trans* configuration is inferred from the *N*-benzyl derivative, *vide supra*.

Flash chromatography also led to the isolation of pyrrole **272**, which has not previously been reported. It was identified from its ^1H NMR spectrum, with the C5-methyl group resonating at δ 2.30 ppm, the *N*-methyl at δ 3.48 and the C3 and C4 pyrrolic protons as doublets at δ 6.06 and δ 5.95 ppm with coupling constants (J = 3.7 Hz), typical for pyrroles. High resolution mass spectroscopy also provided evidence for formation of **272** with a mass to charge ratio of 201.1152 identified, ($\text{C}_{13}\text{H}_{15}\text{NO}^+$ requires 201.1154).

Whilst this could be a key intermediate in the formation of codonopsinine, it had been shown on the C2 and C5 unsubstituted derivative **265** that functionalisation of the pyrroline formed from base-induced elimination was not possible due to the basic amine functionality. Thus, it was attempted to convert this derivative into its carbamate analogue through demethylation by reaction with methyl chloroformate. This transformation has been widely reported in the literature,^{178,179,180} with the most representative conditions being exemplified by Hoppe,¹⁷⁹ involving reaction of methyl chloroformate in refluxing 1,2-dichloroethane.

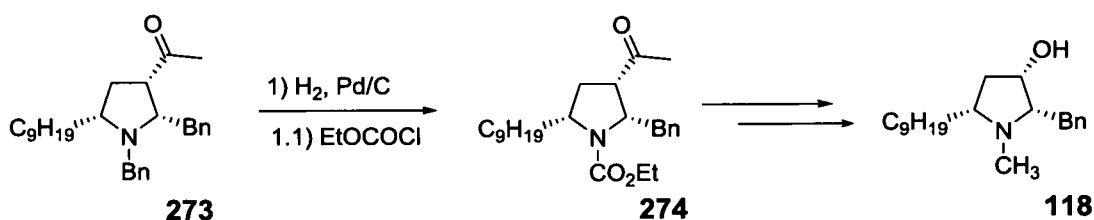
Attempted demethylation of pyrrolidine **264**, derived from sarcosine, formaldehyde and 1,2-*trans*-bisphenylsulfonylethylene with methyl chloroformate under the conditions of Hoppe led to starting material recovery, (Scheme 84).



Scheme 84: Attempted carbamate formation.

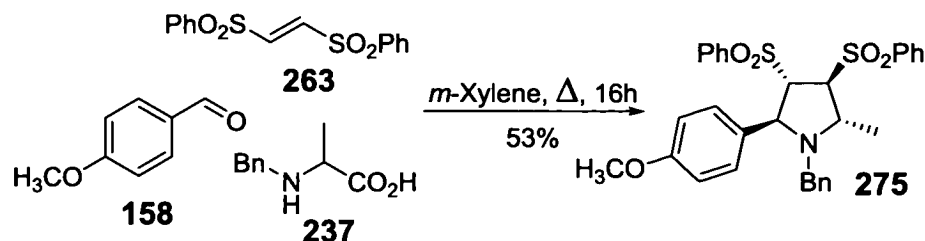
^1H NMR spectral analysis of the crude reaction mixture, worked up by simple evaporation *in vacuo*, showed that the starting material **264** was still present as evidenced by the *N*-methyl group resonance at δ 2.32 ppm.

Thus, due to the inability to convert the *N*-methyl pyrrolidine into its carbamate derivative, *N*-benzyl alanine was investigated in place of *N*-methyl alanine. Overman utilised *N*-benzyl pyrrolidine **273** as a precursor to carbamate **274**, both intermediates in his synthesis of preussin.¹¹⁰ Conversion to the carbamate was achieved by hydrogenation of the *N*-benzyl, followed by reaction with ethyl chloroformate, (Scheme 85).¹¹⁰ LiAlH_4 reduction of the carbamate generates the desired *N*-methyl substituent of the natural product.



Scheme 85: Overman's carbamate formation.¹¹⁰

Three component coupling between *N*-benzyl alanine, 1,2-*trans*-bisphenylsulfonyl ethylene and anisaldehyde in refluxing *m*-xylene gave cycloadduct **275** in 53% yield as a single diastereomer, (Scheme 86).



Scheme 86: *N*-benzyl alanine analogue synthesis.

Correlation to the ^1H NMR spectral data of the *N*-methyl derivative **271** provided evidence for the formation of **275** by the diagnostic doublet, ($J = 6.6$ Hz) at δ 1.09 ppm, for the methyl group at the C5 position of the pyrrolidine. The major difference in the ^1H NMR compared to the *N*-methyl derivative was in the presence of a pair of doublet resonances for the diastereotopic protons of the benzyl group at δ 3.45 and δ 3.27 ppm with a 13.8 Hz coupling constant, indicative of geminal coupling, instead of the *N*-methyl resonance at δ 2.01 ppm. The relative stereochemistry of the pyrrolidine was also determined unequivocally to be all *trans* through single crystal x-ray crystallography, indicating that cycloaddition occurred selectively to give the *anti-exo* cycloadduct, or that epimerisation had occurred (Figure 12).

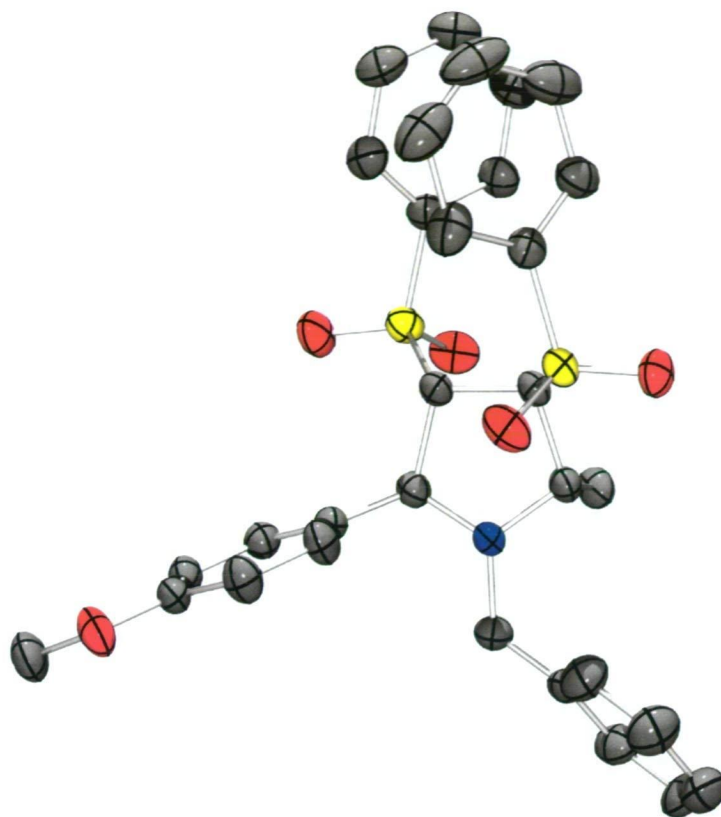
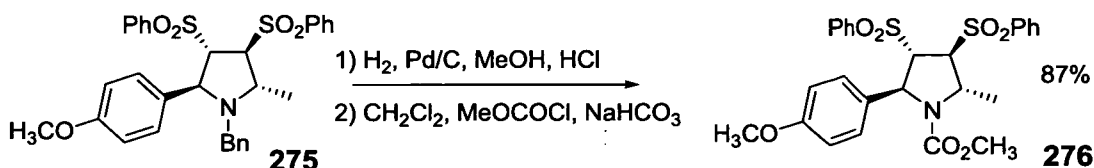


Figure 12: Single crystal X-ray structure of **275**.

Two coupling constants were observable for the protons around the ring. A 7.2 Hz coupling for the proton assigned to be at C2 adjacent to the aromatic ring and the proton at C3, and a 3.6 Hz coupling between the C3 and C4 protons adjacent the phenylsulfonyl groups. This large change between these facially *trans*-oriented protons can be explained through the interesting characteristic of the molecule revealed through the crystal structure in the π -stacking interaction of the phenyl sulfonyl groups. This π -stacking interaction leads to a large difference in the dihedral angle between the C2 and C3 protons (142.9 degrees) compared to the methine protons of C3 and C4 (114.2 degrees). Consequently the coupling constant between the methine protons of C3 and C4 is lower, consistent with the Karplus equation.¹⁸¹

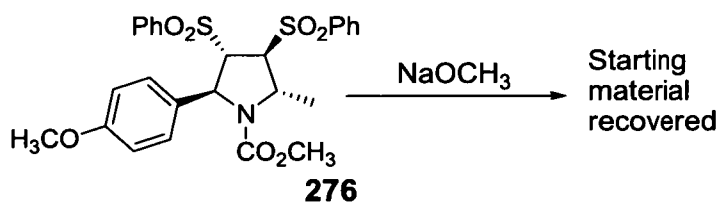
Conversion of *N*-benzyl pyrrolidine **275** to its *N*-methoxycarbonyl analogue **276**, was achieved *via* the method of Overman, by hydrogenolysis of the *N*-benzyl group under hydrogen with Pd/C as catalyst. Reaction of the crude secondary amine product with methyl chloroformate then gave the protected pyrrolidine **276** in 87% yield, (Scheme 87).



Scheme 87: *N*-Benzylamine to carbamate conversion.

^1H NMR spectral analysis of carbamate **276** indicated the presence of a 3:2 mixture of rotamers, as evidenced by the presence of two doublet resonances diagnostic of the C5-methyl group ($J = 6.6$ Hz) at δ 1.11 and δ 0.90 ppm. The ^1H NMR spectrum also showed the loss of the *N*-benzyl methylene resonances of **275** at δ 3.45 and δ 3.27 ppm, which were replaced by rotameric resonances of the methyl group of the carbamate at δ 3.65 and δ 3.73 ppm. ^{13}C NMR spectral analysis also indicated formation of two rotamers, with two resonances for each carbon atom of **276**.

Treatment of **276** with sodium methoxide in dichloromethane/methanol, as per the base induced phenylsulfonyl elimination method of Padwa, was unsuccessful, leading to isolation of unreacted starting material, (Scheme 88).¹⁷²

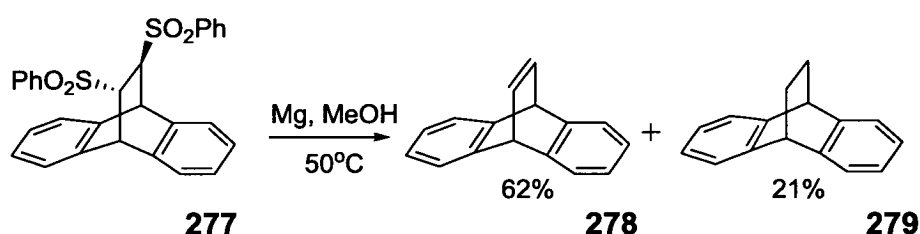


Scheme 88: Attempted base induced elimination.

Given the failure of this elimination, other methods for conversion of our bisphenylsulfonyl pyrrolidines to their corresponding 3-pyrroline analogues were sought. An extensive review of desulfonation reactions has been recently compiled by Nájera.¹⁸² Analysis of the

review shows that the most widely reported method to effect this transformation is the use of a sodium or aluminium amalgam. As mentioned previously, reductive desulfonation with an excess of sodium amalgam was utilised by Carretero to generate 3-pyrrolines from azomethine cycloadducts formed with *trans*-1,2-bisphenylsulfonyl ethylene as dipolarophile.¹⁷¹ However, due to the obvious environmental impact of such methods, a modification by Pak that uses only catalytic mercuric chloride appeared preferential.¹⁸³ Pak's method utilised a magnesium amalgam generated with catalytic mercuric chloride in methanol to effect the desulfonation of several aliphatic derivatives, in short reaction times and high yields.

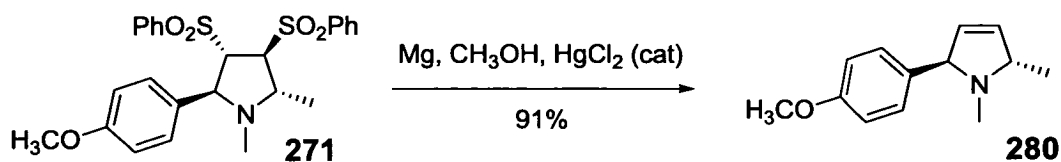
There was also a report of a magnesium in methanol reduction being undertaken on the 1,2-bisphenylsulfonyl derivative **277** by Carpino leading to a mixture of alkene **278** and the aliphatic derivative **279**, (Scheme 89).¹⁸⁴



Scheme 89: Magnesium in methanol desulfonation.¹⁸⁴

Carpino did not require magnesium amalgam to effect the transformation, however we investigated Pak's conditions as they appeared less forcing, as the addition of heat was not required.

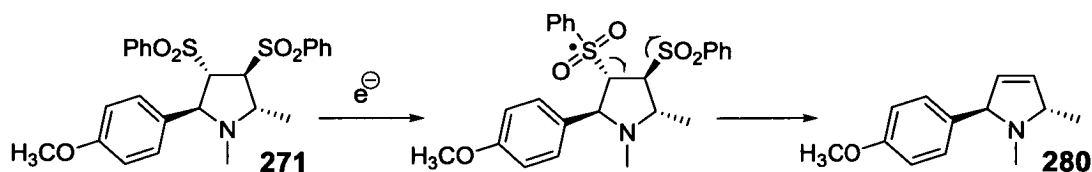
Transferring this reaction technology to the *N*-methyl-3,4-bisphenylsulfonyl codonopsinone precursor **271** led to isolation of the desired 3-pyrroline **280** in excellent yield (91%), (Scheme 90).



Scheme 90: Magnesium in methanol desulfonation.

Spectroscopic identification of **280** was clearly evident by analysis of the ^1H NMR spectrum with two multiplets resonating at δ 5.77-5.79 and δ 5.90-5.92 ppm, evidence of alkenyl protons. The product had also not undergone β -elimination to the corresponding pyrrole, as the methyl group at C5 of the ring was still a doublet at δ 1.20 ppm with a coupling constant of 6.6 Hz.

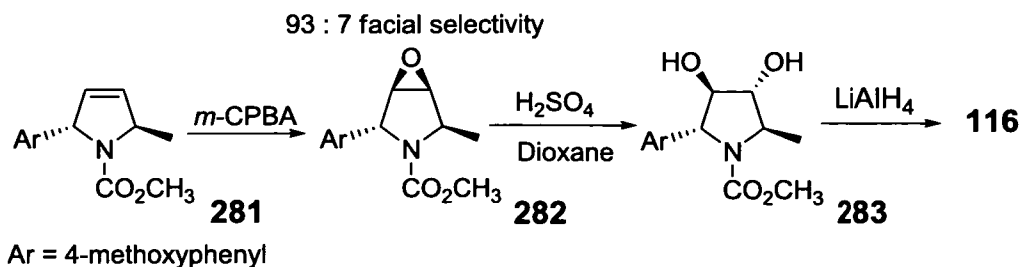
However, as opposed to Carpino's report, we exclusively obtained the alkene, which is believed to have been formed by β -elimination of the radical formed from electron addition to the first sulfonyl group, (Scheme 91).



Scheme 91: Proposed mechanism of magnesium in methanol desulfonation.

Thus we have developed an alternative method to enable *trans*-1,2-bisphenylsulfonyl ethylene to act as an acetylene equivalent for use in azomethine ylide chemistry.

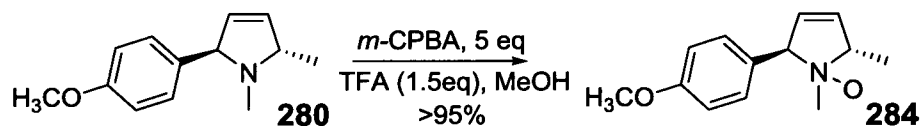
Synthesis of codonopsinine from 3-pyrroline **280**, as can be seen structurally, requires dihydroxylation of the alkene. However, as previously mentioned, dihydroxylation of pyrrolines is difficult due to the presence of the amine. Therefore we decided to investigate an epoxidation/ring opening route to the 3,4-dihydroxypyrrolidine core, similar to the route used by Correia in his synthesis of codonopsinine, and by Wang for his synthesis of codonopsine, (Scheme 92).^{106,107}



Scheme 92: Correia's approach towards codonopsinine.¹⁰⁶

Correia reported good facial selectivity for epoxidation of **281** yielding epoxide **282** as the major product, which underwent acid mediated ring opening to give the desired *trans*-diol **283**. Reduction with LiAlH_4 then yielded the target natural product. Therefore, if epoxidation of the tertiary amine **280** could be achieved, ring opening of the epoxide should yield the target natural product. Epoxidation of phenylsulfonyl substituted pyrrolidine **265** by the method of Muraoka was not successful, however epoxidation of **280** was attempted under these conditions, due to the fact the alkene should be more nucleophilic without a phenylsulfonyl substituent.

Treatment of **280** with five equivalents of *m*-CPBA in the presence of TFA to protonate the amine led to isolation of *N*-oxide **284**, despite the protonation of the amine, (Scheme 93).¹⁷⁵



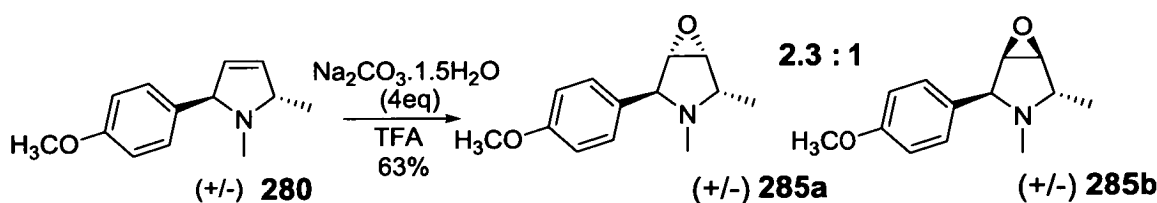
Scheme 93: Epoxidation towards codonopsinine.

N-Oxide formation was evident from the change in chemical shift in the ^1H NMR spectrum of the protons closest to the nitrogen atom. The *N*-methyl group shifted from δ 2.19 in **280** to δ 3.00 ppm in **284**, and the C5 methyl group doublet had shifted from δ 1.19 ppm in **280** to δ 1.63 ppm in **284**. Mass spectroscopy was also consistent with *N*-oxide formation, with the $[\text{M}+\text{H}]^+$ ion of 220 observed.

Thus, a stronger epoxidation agent was desired and trifluoroperacetic acid was investigated. Trifluoroperacetic acid is commonly formed by reaction of trifluoroacetic

anhydride with 90% hydrogen peroxide.¹⁸⁵ However, as we are unable to access 90% hydrogen peroxide, we turned to a method of generating trifluoroperacetic acid reported by Olah, as used for Baeyer-Villiger oxidations.¹⁸⁶ Olah reported that *in situ* formation of the peracid could be achieved by adding sodium percarbonate to trifluoroacetic acid.

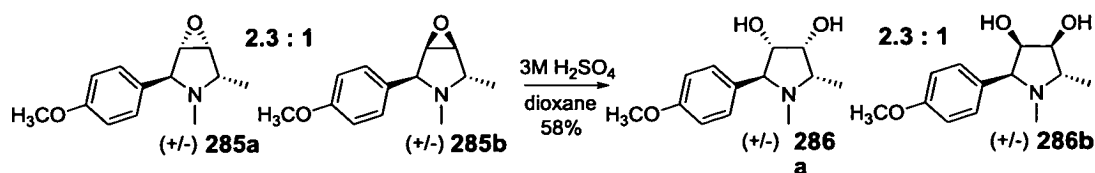
Reaction of pyrroline **280** with four equivalents of sodium percarbonate in trifluoroacetic acid led to an inseparable 2.3 : 1 ratio of diastereomeric epoxides **285a** and **285b** in 63% yield, (Scheme 94).



Scheme 94: Epoxidation of pyrroline **280**.

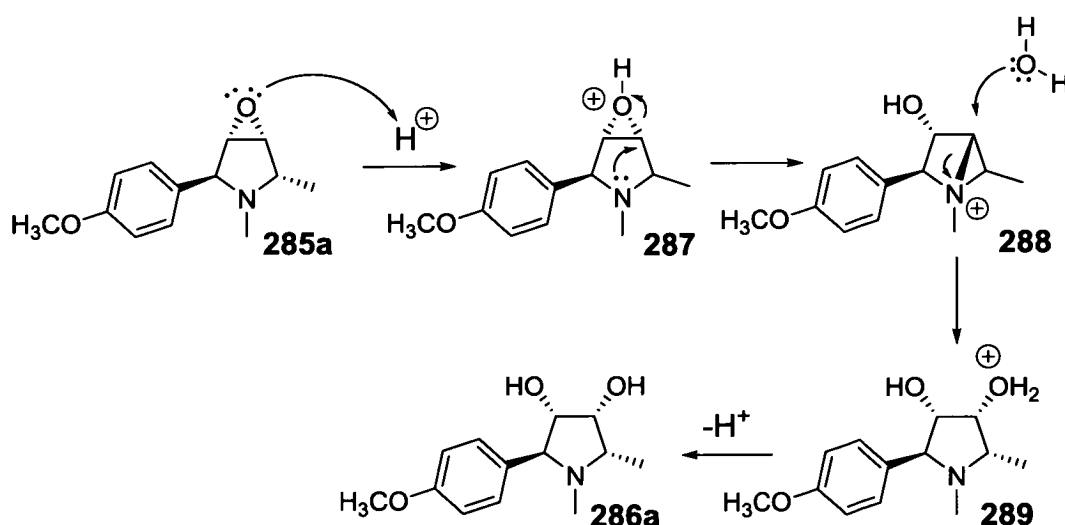
Epoxidation was confirmed through mass spectroscopic analysis with an [M]⁺ of 219 found. The facial selectivity was determined by the integration of the C5 methyl resonances for each diastereomer in the ¹H NMR spectrum at δ 1.02 and δ 1.25 ppm. Unfortunately, overlap of the protons bound to the pyrrolidine ring resulted in no coupling constants being determinable, and therefore the major isomer is implied to be **285a**. This is based on the report of Correia; who found that addition of the oxygen to the alkene occurred from the least hindered face, that opposite the aromatic ring.¹⁰⁶ However our facial selectivity was much lower.

Ring opening of the diastereomeric mixture of epoxides **285** by refluxing in dioxane with ten equivalents of 3M sulfuric acid, the conditions reported by Correia, led to a 58% yield of a 2.3 : 1 mixture of diastereomers of codonopsinine **286a** and **286b**, (Scheme 95).¹⁰⁷



Scheme 95: Epoxide ring opening.

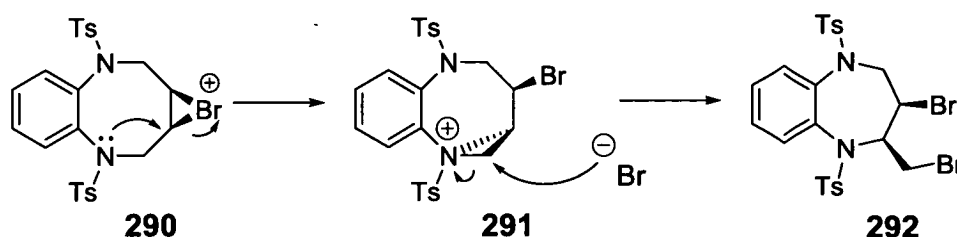
Analysis of the ^1H NMR spectrum showed the diagnostic C5 methyl resonances at δ 0.86 and δ 1.23 ppm retained an integration ratio 1 : 2.3 respectively, and MS analysis gave the required $[\text{M}+\text{H}]^+$ peak of 238. However, interestingly neither diastereomer synthesised was the expected (\pm) -codonopsinine, as comparison of the obtained ^1H and ^{13}C NMR spectra to the those reported by Kibayashi in his synthesis of the four codonopsinine diastereomers, featuring a C3-C4 *trans*-diol relationship, showed there was no correlation.⁸⁹ Therefore, we hypothesise that the ring opening did not lead to formation of *trans* diol, as would be anticipated for the ring opening of an epoxide, but must feature a *cis* configuration. Unfortunately no isomer of codonopsinine with a *cis*-diol has been previously synthesised. We propose that an assisted ring opening occurred, due to the presence of the nucleophilic amine, (Scheme 96).



Scheme 96: Proposed mechanism of epoxide ring opening.

Antiperiplanar attack of the nucleophilic nitrogen would lead to bicyclic aziridine **288**, which would undergo ring opening to yield the *cis*-diol. Unfortunately no examples of such a

mechanism were found in the literature, which is most likely a result of the difficulty in epoxidising the tertiary amine. Some literature precedence is present for the formation of an aziridine when an amine is β to a halonium ion. Paquette recently reported the ring opening of halonium ion **290** to give *cis*-oriented dibromide **292** through the formation of aziridinium intermediate **291**.¹⁸⁷ Paquette proposed the bromide opened the aziridine at the least sterically-congested position, which led to the ring rearrangement, (Scheme 97).

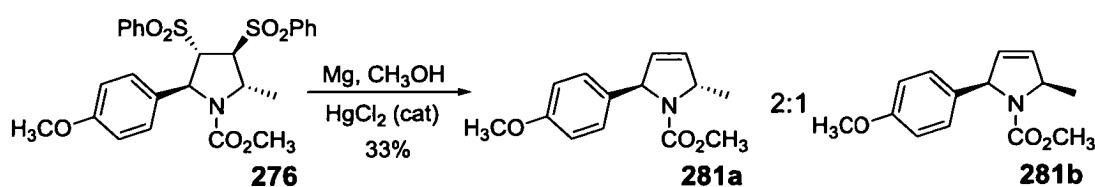


Scheme 97: Paquette's bromonium ring opening via nucleophilic β -nitrogen.¹⁸⁷

Given the ring-opening of epoxides **285a** and **285b** had not occurred as expected to yield the desired *trans* diol, it was proposed that pyrrolidine carbamate **276**, which was resistant to base-induced elimination could undergo desulfonation by the magnesium in methanol reduction to yield its corresponding pyrroline derivative, which had been previously synthesised by Correia in his codonopsinine synthesis.¹⁰⁶

2.5.6 Total formal synthesis of codonopsinine

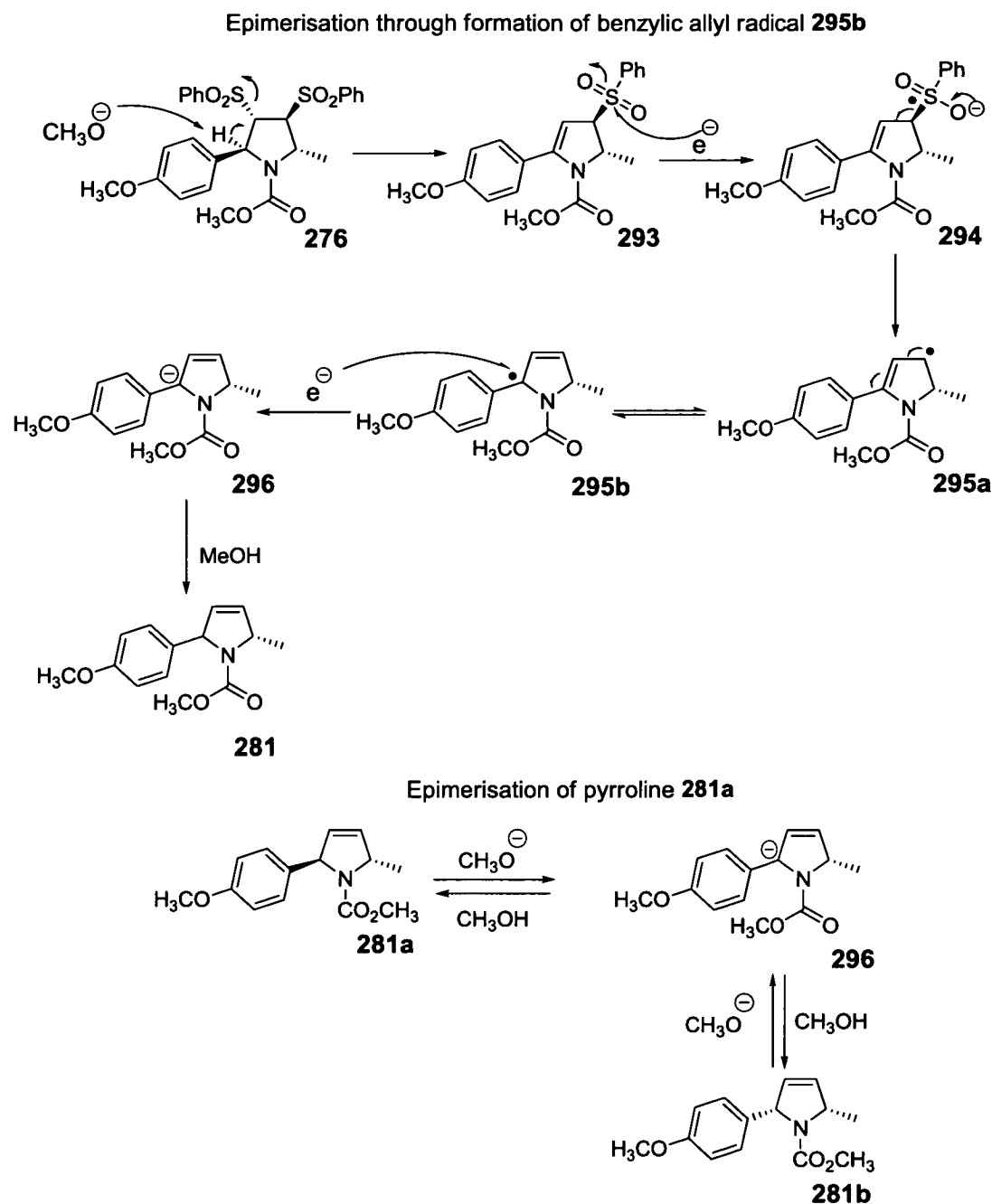
Treatment of the bisphenylsulfonyl methyl carbamate **276** with ten equivalents of magnesium and catalytic mercuric chloride in methanol gave a 33% yield of pyrrolines **281a** and **281b** as a 2:1 mixture after chromatography, (Scheme 98).



Scheme 98: Total formal synthesis of codonopsinine.

Desulfonation of the carbamate **276**, compared to the *N*-methyl derivative **271**, did not occur selectively and epimerisation occurred, leading to a 2:1 ratio of the *trans*: *cis* diastereomers **281a** and **281b**, which were inseparable by flash chromatography. The major isomer **281a**, present as a mixture of rotamers, was spectroscopically identical to that reported previously by Correia.¹⁰⁶ The minor *cis*-isomer **281b** was identified by the presence in the ¹H NMR spectrum of a pair of doublets at δ 1.23 and δ 1.30 ppm, assigned as rotameric resonances of the C5 methyl group.

Differing from the reductive elimination of the phenylsulfonyl groups of tertiary amine **271** which gave a single 3-pyrroline diastereomer, (Scheme 91), we propose the epimerisation occurred due to either competing elimination and reductive elimination pathways, or through epimerisation of product pyrroline **281a** (Scheme 99).



Scheme 99: Proposed mechanisms for epimerisation.

This epimerisation was surprising, and requires further research to understand the processes leading to this result. We propose the epimerisation of the pyrrolidine leading to the two diastereomeric pyrrolines **281a** and **281b** stems from the higher acidity of the C2 methine proton due to the adjacent *N*-methoxycarbonyl group in **276**, compared to the *N*-methyl pyrrolidine **271**. Thus, under the desulfonation conditions, the magnesium methoxide could deprotonate at C2, leading to β -elimination of the C3 phenyl sulfonyl

group, giving **293**. After elimination of the second phenyl sulfonyl group, this would give allylic radical **295a**, which would be in resonance with **295b**. Addition of an electron and protonation would give a mixture of diastereomeric pyrrolines **281**.

Alternatively, desulfonation as per Scheme 91 would yield 3-pyrroline **281a**, which could undergo epimerisation due to the relatively acidic C2 methine proton. The deprotonation of this position in *N*-methoxycarbonyl-3-pyrrolines has been reported with LDA,⁶⁹ and it is conceivable that magnesium methoxide can coordinate to the carbonyl group and deprotonate in an intramolecular manner. To test whether this second mechanism is occurring, formation of **281a** by a different synthetic protocol, then treatment under the reaction conditions would determine if this pathway for epimerisation is possible.

Thus, we had obtained a mixture of the *trans* and *cis* diastereomers of the carbamate previously elaborated by Correia to (-)-codonopsinine, therefore effecting a formal synthesis of the natural product.¹⁰⁶ This mixture was also similar to the mixture previously obtained by Wang in his synthesis of codonopsine.¹⁰⁷

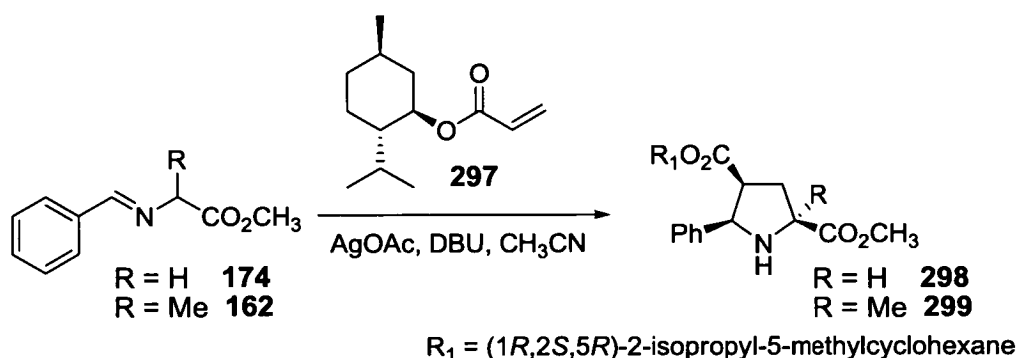
2.6 Asymmetric azomethine ylide cycloadditions

Whilst achieving a route to generate pyrrolidine alkaloids through azomethine cycloaddition chemistry, the previously reported work gave only racemic products, and thus it is desirable to improve upon these methods to yield enantiopure products. There has been considerable work performed studying the construction of enantiopure pyrrolidine ring systems *via* azomethine ylide chemistry. Recent reviews by Pandey *et al.*¹¹⁹ and Harwood and Vickers,¹¹⁸ highlight the many different approaches to achieve this goal, including the use of chiral dipolarophiles, chiral azomethine ylides and chiral catalysts that coordinate the azomethine ylide or the dipolarophile to introduce asymmetry into the pyrrolidine ring system. These reviews also cover the large body of literature on intramolecular asymmetric azomethine chemistry.

2.6.1 Asymmetric stabilised azomethine ylide chemistry

To determine if we could develop an asymmetric approach to pyrrolidines, we decided to extend the reaction of both stabilised and non-stabilised azomethine ylides to chiral dipolarophiles. Grigg has reported the reaction of stabilised azomethine ylides coordinated to silver ions with chiral dipolarophile (-)-menthyl acrylate for asymmetric induction.^{188, 176,126}

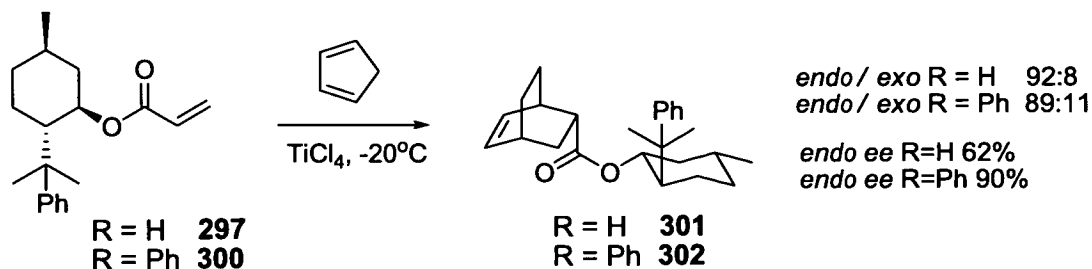
Grigg reported that reaction of (-)-menthyl acrylate and the azomethine ylides generated from imines **174** and **162** yielded single homochiral cycloadducts **298** and **299** respectively, (Scheme 100).



Scheme 100: Grigg's asymmetric azomethine cycloadditions.¹⁷⁶

The homochirality of the cycloadducts was determined through HPLC and optical rotation measurements after crystallisation.

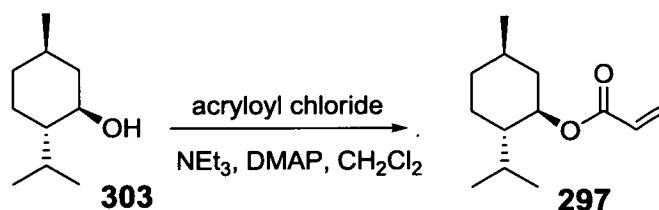
This was surprising, as menthol is not usually the most effective chiral auxiliary. For example, the Diels-Alder reaction between (-)-menthyl acrylate and cyclopentadiene gives a 92:8 *endo*:*exo* selectivity, where after hydrolysis *endo* adduct **301** was found to have a 62% ee, (Scheme 101).¹⁸⁹ This compares with the (-)-8-phenylmenthol case where the *endo* : *exo* selectivity was similar, however the ee of **302** was found to be 90%.¹⁸⁹



Scheme 101: Diels-Alder reaction of (-)-menthyl acrylate.¹⁸⁹

Thus, with this precedent in the literature we investigated the use of (-)-menthyl acrylate for asymmetric induction using our lithium bromide based cycloaddition protocol.

Due to limited commercial availability, (-)-menthyl acrylate (**297**) was prepared from L-menthol **303** and acryloyl chloride in 67% yield, (Scheme 102).

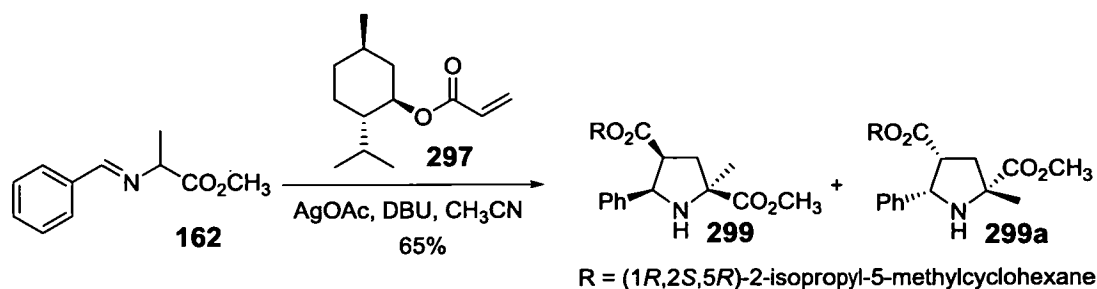


Scheme 102: Synthesis of (-)-menthyl acrylate.

Formation of the acrylate was determined by ^1H NMR analysis, which showed the characteristic acrylate resonances at δ 5.79, 6.10 and 6.38 ppm, coupling as doublet of doublets.

Reaction of dipolarophile **297** with imine **162** and lithium bromide in refluxing THF for 20h did not lead to any cycloadduct being observed by analysis of the crude ^1H NMR spectrum, indicating unreacted acrylate was isolated from the reaction. This is not an entirely surprising result as acrylates are less reactive than fumarate, having only one activating group. The rate of azomethine cycloaddition reaction has also been shown to decrease with increasing steric bulk of the dipolarophile.¹⁷⁶

As way of confirmation we repeated Grigg's reaction under his exact conditions and obtained a 65% yield of cycloadducts **299** and **299a**, (Scheme 103).



Scheme 103: Cycloaddition with (-)-menthyl acrylate.

Grigg reported that his cycloadditions were highly enantioselective, effectively homochiral, based on analysis of the ¹³C NMR spectra of the crude reaction product, where he reported only one diastereomer was visible. However, upon exactly repeating his reaction conditions, we found there to be a trace amount of a second diastereomer **299a**, clearly visible in the ¹³C NMR as a second set of peaks, (Figure 13). We have tentatively proposed the second isomer is the endo cycloadduct **299a**, however it is conceivable that the second diastereomer is the exo cycloadduct of **299**. Surprisingly, the ¹H NMR spectrum did not distinguish the second isomer. Without ¹H NMR integration it was not possible to determine the exact amounts of each diastereomer, however the ¹³C NMR spectrum indicated an approximately 9:1 ratio of diastereomers **299** and **299a**. Grigg did not report ¹³C NMR data in his paper, however he commented that analysis of the crude ¹³C NMR gave evidence that only one diastereomer was obtained. He also reported crystallisation of the crude product, which if prior to ¹³C NMR analysis, resulted in removal of the minor diastereomer. ¹³C NMR of our purified cycloadduct (silica gel chromatography) showed twenty two carbon resonances for the major diastereomer, whilst twenty of the twenty two resonances of the minor diastereomer were visible, (Figure 13).

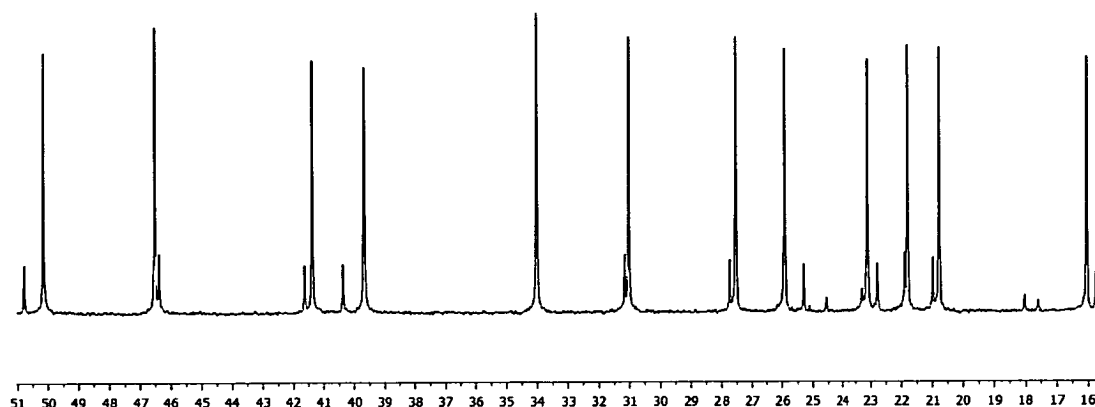
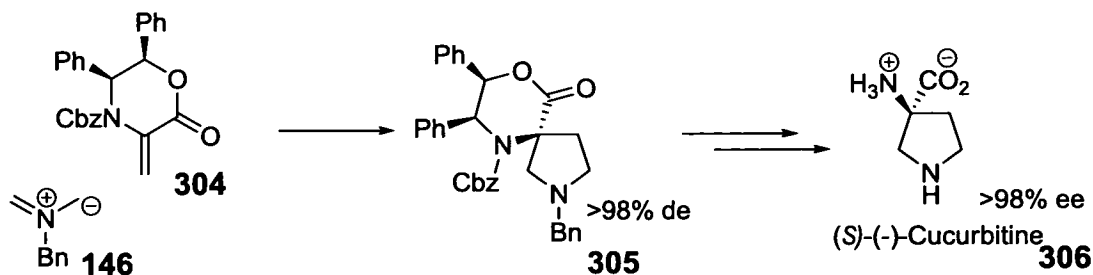


Figure 13: Partial ^{13}C NMR spectrum of **299** and **299a**.

Whilst 9:1 is a reasonably high asymmetric induction for menthol in a cycloaddition, the extra steric bulk of the ester group within the dipolarophile makes it less reactive and consequently unreactive under the mild lithium bromide conditions.

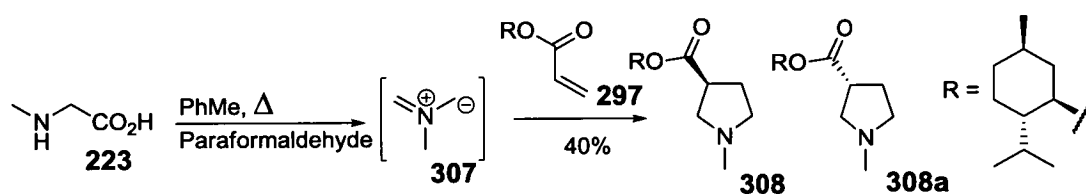
2.6.2 Asymmetric non-stabilised azomethine ylide chemistry

Given that (-)-menthyl acrylate was unable to induce high levels of diastereoselectivity (i.e. >95:5) with a stabilised azomethine ylide, we decided to investigate its potential with non-stabilised azomethine ylides. The extensive studies into asymmetric cycloaddition with non-stabilised ylides have also been covered by the reviews mentioned previously.^{119,118} One of the earliest successes employing a chiral dipolarophile was the group of Williams' synthesis of (S)-(-)-cucurbitine **306**, a naturally occurring amino acid found in the seeds of several varieties of pumpkin.¹⁹⁰ Williams utilised a highly diastereoselective cycloaddition between the azomethine ylide **146**, generated by desilylation of Padwa's reagent (*N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine), and chiral dipolarophile **304**, (Scheme 104).



Scheme 104: Williams (S)-(-)-cucurbitine synthesis.¹⁹⁰

To investigate how (-)-menthyl acrylate performs in a diastereoselective azomethine cycloaddition with a non-stabilised azomethine ylide, a mixture of sarcosine, paraformaldehyde and (-)-menthyl acrylate was heated under reflux in toluene under Dean-Stark conditions. Azomethine ylide **307** was hence trapped with menthyl acrylate, leading to a 1:1 mix of diastereomeric cycloadducts **308** and **308a** that were inseparable by flash chromatography in 40% yield, (Scheme 105).



Scheme 105: Initial decarboxylative test with (-)-menthyl acrylate.

The ^1H NMR spectrum did not clearly show both diastereomers, however no acrylate resonances remained, and the distinctive resonance of the methine proton (ddd) adjacent to the oxygen of the menthol moiety was present at δ 4.62 ppm in the newly formed pyrrolidine, shifted from δ 4.75 ppm in the acrylate. While analysis of the ^1H NMR was inconclusive, the ^{13}C NMR spectrum clearly indicated a mix of two diastereomers **308** and **308a** in an approximately 1:1 ratio, (Figure 14).

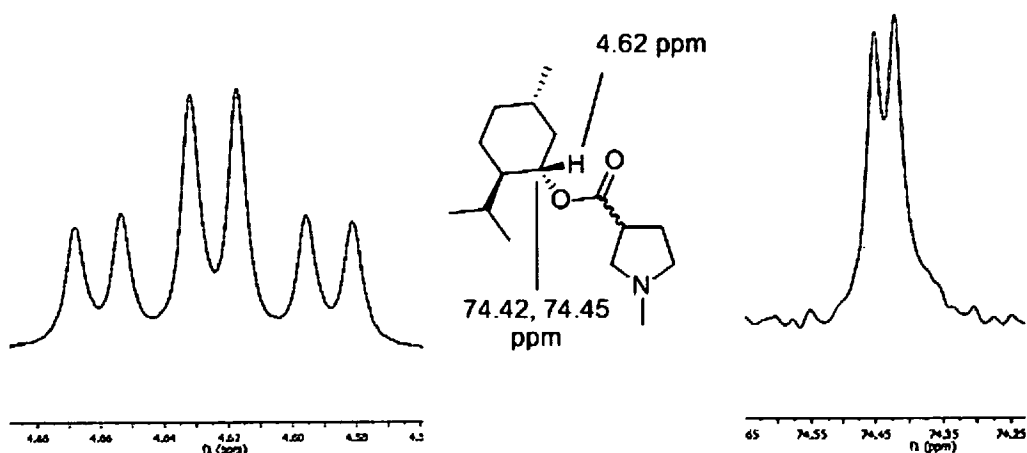
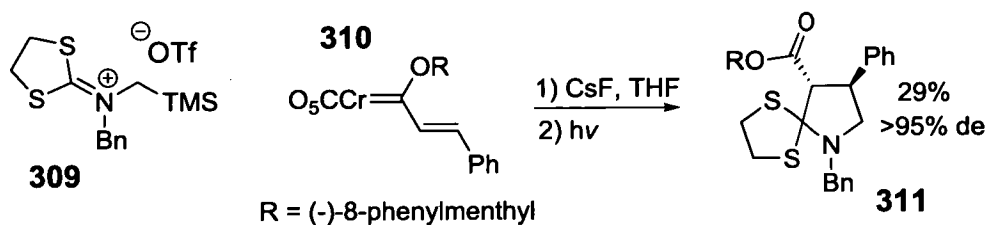


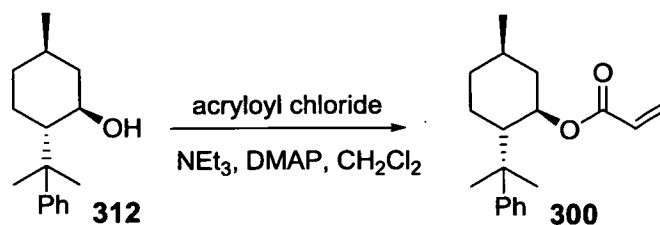
Figure 14: ^1H and ^{13}C resonances of methine adjacent to oxygen in **308** and **308a**.

Given the failure of (-)-menthyl acrylate to induce diastereoselectivity we decided to investigate whether the acrylate derived from Corey's chiral auxiliary, (-)-8-phenylmenthol, would be a more powerful chiral auxiliary for this cycloaddition. As mentioned above in Scheme 101, there is precedence from Diels-Alder chemistry for enhanced diastereoselectivity of (-)-8-phenylmenthyl acrylate compared to (-)-menthyl acrylate.¹⁸⁹ This enhanced specificity is believed to be due to π -stacking of the phenyl ring favouring one face of the acrylate.¹⁹¹ There is some precedence for asymmetric induction of addition to an azomethine ylide using an (-)-8-phenylmenthol derived dipolarophile, with **310** reported to undergo azomethine cycloaddition with >95:5 diastereoselectivity to the ylide derived from desilylation of **309**, (Scheme 106).¹⁹²



Scheme 106: (-)-8-phenylmenthyl acrylate azomethine ylide asymmetric induction precedent.¹⁹²

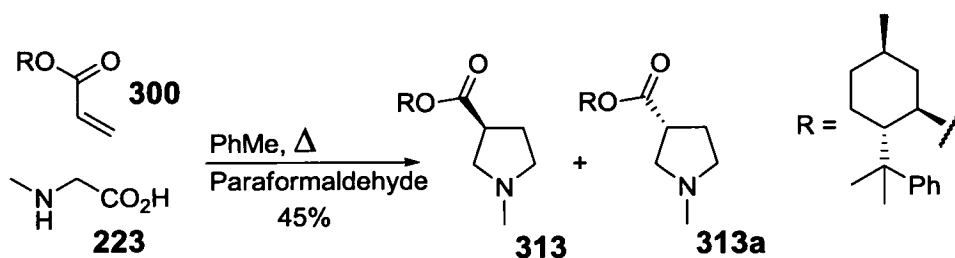
(-)-8-Phenylmenthyl acrylate was generated as per its (-)-menthol analogue by the reaction of acryloyl chloride with (-)-8-phenylmenthol **312** (which was prepared using the method of Ort as part of an undergraduate course at the University of Tasmania), (Scheme 107).¹⁹³



Scheme 107: Synthesis of (-)-8-phenylmenthyl acrylate.

Formation of the acrylate **300** was confirmed by comparison of the NMR spectra with that of the menthol analogue **299**. The methine proton adjacent to the oxygen, with diagnostic doublet of doublet of doublets splitting, was shifted to δ 4.86 ppm compared to δ 4.75 ppm for the (-)-menthyl derivative due to extra deshielding from the phenyl ring.

Reaction of (-)-8-phenylmenthyl acrylate, sarcosine and formaldehyde surprisingly gave a similar result to the (-)-menthol auxiliary, with cycloadducts **313** and **313a** being formed in 45% yield, (Scheme 108).

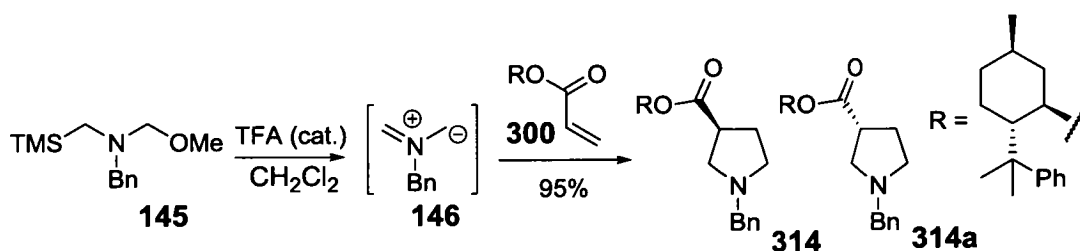


Scheme 108: (-)-8-Phenylmenthyl acrylate in a decarboxylative cycloaddition.

Again the ^1H NMR was inconclusive as to the formation of 2 diastereomers; however, the ^{13}C NMR spectrum showed a mixture with two sets of signals in an approximately 1:2 ratio for compounds **313** and **313a**. Cycloaddition was again shown to have occurred through the distinctive shift of the methine proton of the cyclohexyl ring bound to the oxygen at δ

4.80 ppm, with loss of the three acrylate resonances between δ 5.5 and 7.1 ppm. The cycloadduct ^1H NMR also showed a singlet methyl resonance at δ 2.38 ppm for the *N*-methyl group, as well as two multiplet resonances integrating for the four protons adjacent to the nitrogen between δ 2.45 - 2.55 and 2.78 - 3.02 ppm.

Given there appeared to be an improvement in the diastereoselectivity between (-)-menthyl and (-)-8-phenylmenthyl acrylates, we thought that lower reaction temperatures may improve the diastereoselectivity, as there are numerous precedents in the literature for temperature playing a major factor in stereooutcomes. Generation of azomethine ylide **307** from sarcosine and paraformaldehyde requires high temperatures to undergo decarboxylation and ylide formation, therefore we turned to a desilylation method of azomethine ylide generation. Achiwa¹²⁴ published an alternative procedure to Padwa's¹²² fluoride-based desilylation of *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine **145**, which simply uses a catalytic amount of TFA in dichloromethane to generate ylide **146**, (Scheme 109). The *N*-benzyl substituted ylide **146** is generated at room temperature using these conditions, compared to the toluene reflux temperature required to generate ylide **307** by decarboxylation.

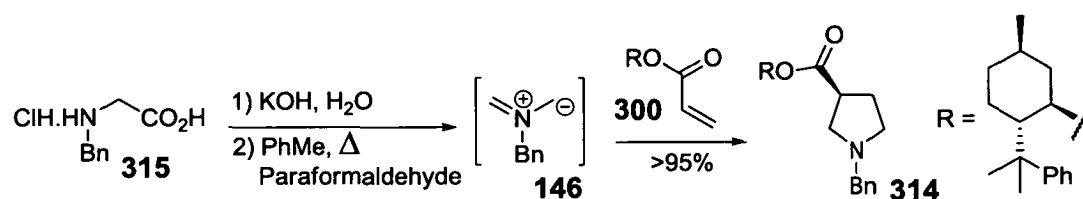


Scheme 109: (-)-8-Phenylmenthyl acrylate cycloaddition with a non-stabilised ylide.

Under these conditions reaction with (-)-8-phenylmenthyl acrylate led to a 1:1 mix of diastereomers **314** and **314a** in an improved yield of 95%, (Scheme 109). Surprisingly, lowering the temperature resulted in lower diastereoselectivity. Again the ratio of diastereomers could not be confirmed by ^1H NMR analysis, however in this case the

methine proton at $\approx \delta$ 4.8 ppm was not a clear doublet of doublet of doublet of doublets and was instead a multiplet. The ^{13}C NMR spectrum confirmed the formation of the two diastereomers, showing an \approx 1:1 peak height for each resonance. An attempt to generate ylide **146** and undergo cycloaddition at the lower temperature of -18°C did not lead to any cycloaddition occurring.

Given that the lower diastereoselectivity at room temperature occurred with *N*-benzyl ylide **146** compared with *N*-methyl ylide **307** formed through decarboxylation, *N*-benzyl glycine was used instead of sarcosine to generate *N*-benzyl azomethine ylide **146** at higher temperature to confirm these results, (Scheme 110).

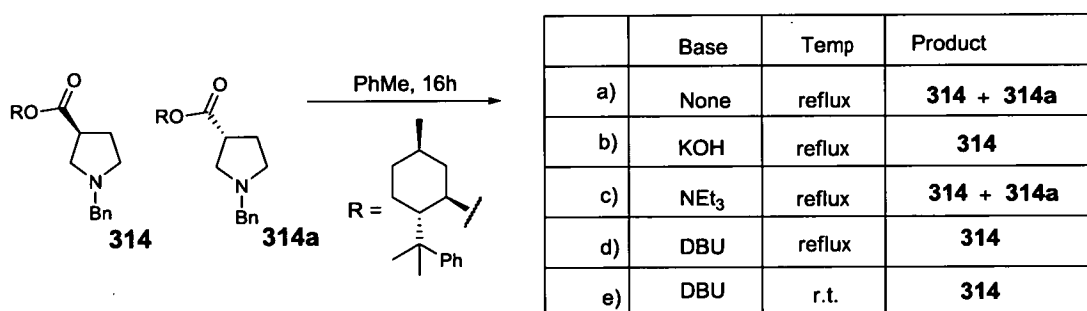


Scheme 110: (-)-8-Phenylmenthyl acrylate cycloaddition with a non-stabilised ylide.

As *N*-benzyl glycine is available commercially as its hydrochloride salt **315**, it was neutralised with potassium hydroxide in water and evaporated to dryness prior to cycloaddition. Reflux in toluene of the resultant *N*-benzylglycine and potassium chloride mixture with paraformaldehyde and acrylate surprisingly isolated a single diastereomer **314**. The ^1H NMR was identical to that previously observed, however there was only one set of resonances in the ^{13}C NMR spectrum. Thus, the reaction had proceeded with high diastereoselectivity. The reaction was repeated to ensure nothing anomalous had occurred and the same results were obtained. Given the presence of an epimerisable centre in the product, it was thought that perhaps the *N*-benzyl derivative was more prone to epimerisation, and given that the product **314** contains a basic nitrogen atom, that under the conditions of refluxing toluene epimerisation could occur.

Hence, the 1:1 mix of diastereomers **314** and **314a**, obtained from (-)-8-phenylmenthyl acrylate and ylide **146** generated from the Padwa reagent, was heated in toluene for 16 h. This did not lead to an observable epimerisation from analysis of the ^{13}C NMR.

As the pyrrolidine itself was not a strong enough base to perform epimerisation, it was then proposed that there may have been a small amount of potassium hydroxide present from the neutralisation of the amino acid hydrochloride salt. Thus, epimerisation was attempted with a catalytic amount of potassium hydroxide added to a solution of the diastereomeric mix of pyrrolidines **314** and **314a** in toluene at reflux. Analysis of the ^{13}C NMR of the product revealed only one diastereomer, confirming that a small amount of potassium hydroxide could in fact cause epimerisation. Further experiments were then performed to determine the strength of base required to induce epimerisation, (Scheme 111).



Scheme 111: Base catalysed epimerisation of **314a** to **314**.

Triethylamine did not result in epimerisation at elevated temperature; however stronger base DBU gave complete epimerisation to **314**, even at room temperature.

The epimerisation was believed to have occurred successfully through selective reprotonation from the least hindered face of the enolate **316** formed by deprotonation of the pyrrolidine, due to the steric blocking of the other face by the (-)-8-phenylmenthyl group π -stacking with the enolate, which we predict to give the (*S*) configured stereocentre, (Figure 15).¹⁹¹

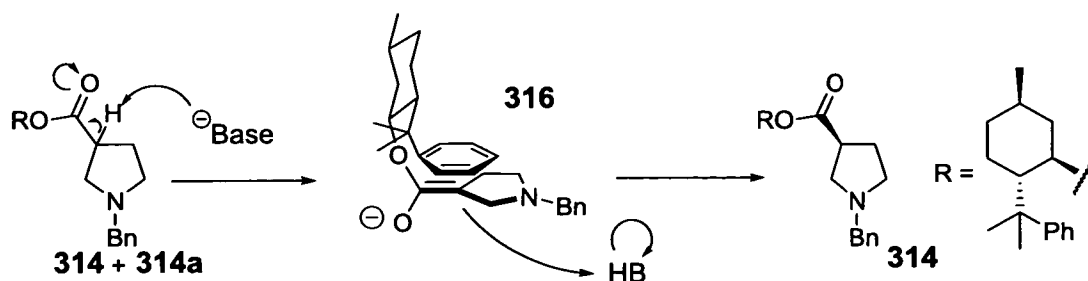
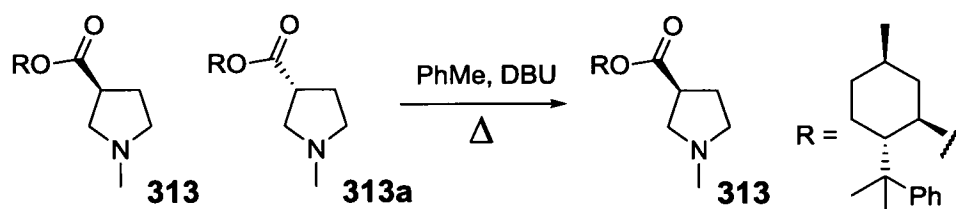


Figure 15: Epimerisation of pyrrolidine carboxylates.

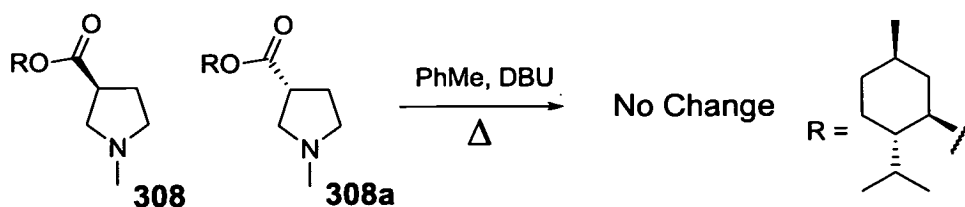
Thus to determine if the *N*-benzyl group was somehow involved in the π -stacking interactions and was therefore important in this epimerisation, the 2:1 mixture of *N*-methyl pyrrolidine diastereomers **313** and **313a** were subjected to epimerisation conditions, (Scheme 112).



Scheme 112: Base catalysed epimerisation of **313** to **313a**.

As with the *N*-benzyl derivative the *N*-methyl derivative underwent epimerisation to form a single diastereomer. ^{13}C NMR spectral analysis showed that the pair of resonances representing each carbon for both diastereomers became a single resonance. Interestingly, the major isomer from the cycloaddition disappeared, leading to **313**.

Thus, it was considered that the (-)-menthyl acrylate cycloadducts **308** and **308a** may also be able to undergo base catalysed epimerisation. Heating an approximately 1:1 mixture of cycloadducts **308** and **308a** in toluene in the presence of DBU gave no change when analysed by ^{13}C NMR spectroscopy, (Scheme 113).



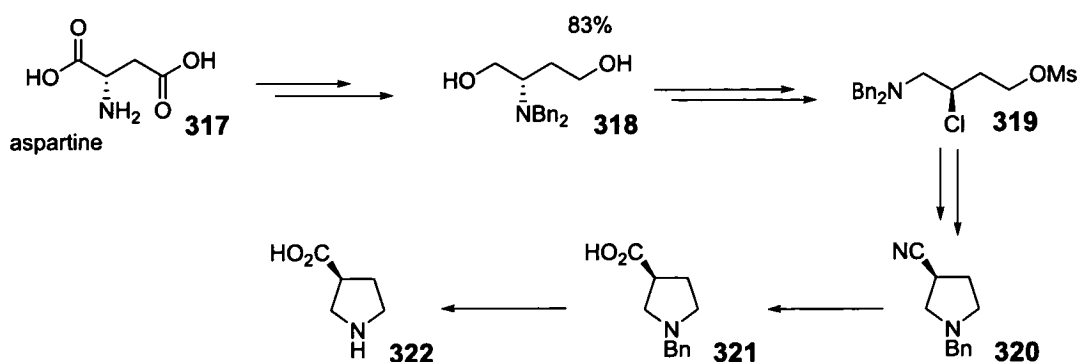
Scheme 113: Attempted base catalysed epimerisation of **308** and **308a**.

It was not entirely surprising, that this did not lead to any observable change in the diastereomeric mixture, as unlike (-)-8-phenylmenthyl esters, the (-)-menthyl derivatives are not as effective at controlling the facial selectivity for the approach of an electrophile to an enolate.

2.6.3 (*S*)- β -Proline

Attention turned to the utilisation of this excellent epimerisation result for the targeting of some biologically-important molecules. One such molecule, important in studies of peptide mimetics, is β -proline.¹⁹⁴ Despite its importance in biomedical chemistry, there have been very few syntheses of enantiopure β -proline reported.^{195,196,197,198}

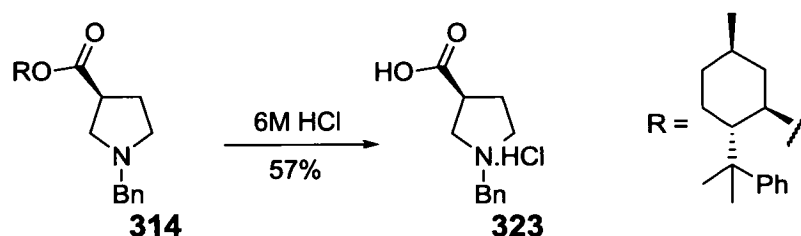
One of these reported syntheses is Gmeiner's enantiospecific pathway from aspartic acid **317**, which he elaborated to chiral amino-nitrile **320**, chemically very similar to our epimerised amino-ester **314**.¹⁹⁶ Gmeiner then hydrolysed the amino nitrile **320** with hydrochloric acid to yield the *N*-benzyl acid **321**, and hydrogenation over palladium hydroxide yielded (*S*)- β -proline **322** in 49% overall yield over 7 steps, (Scheme 114).



Scheme 114: Gmeiner's β -proline synthesis.¹⁹⁶

The *N*-benzylamino acid **321** was isolated as its hydrochloride salt; however the free amino acid was obtained by ion-exchange chromatography on Amberlite IRA 400. Hence, if we analyse pyrrolidine **314**, two steps are required to complete a synthesis of β -proline, those being hydrolysis of the (-)-8-phenylmenthol ester to acid **321**, and debenzylation. This also allows the absolute stereochemistry of **314** to be determined, confirming if the (5) configured stereogenic centre is formed as predicted. Indeed, there has been a reported racemic synthesis of β -proline utilising ethyl acrylate *via* the same synthetic pathway that we propose.¹⁹⁹

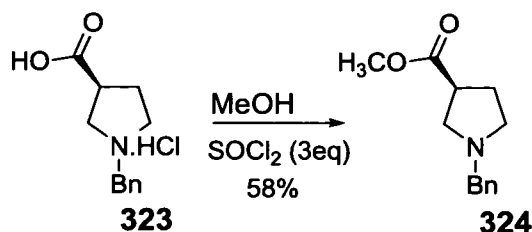
The acid catalysed hydrolysis of **314** was successful, with the *N*-benzylamino acid hydrochloride **323** being formed in 57% yield, (Scheme 115).



Scheme 115: Formal synthesis of β -proline.

Work up of the reaction was modified from the method reported by Gmeiner for hydrolysis of nitrile **320** by introducing an ether wash of the hydrolysis. This allowed the recovery of the chiral auxiliary (-)-8-phenylmenthol from the reaction mixture in 77% recovered yield. This is an important result, as (-)-8-phenylmenthol is expensive to purchase commercially, or requires synthesis from pulegone, therefore recycling is important, particularly for a large scale synthesis. While Gmeiner isolated the free base *N*-benzyl- β -proline, we isolated *N*-benzyl- β -proline as its hydrochloride salt. Interestingly, protonation of the amine on either face of the pyrrolidine resulted in two diastereomers being observed by ¹³C NMR analysis. Whilst this completes a formal synthesis of β -proline as only debenzylation is required, for simplicity we converted the *N*-benzyl acid to the known methyl ester **324** by

reaction with methanolic HCl to determine the optical rotation, and to confirm the formation of the (*S*)-configured stereocentre, (Scheme 116).



Scheme 116: Esterification of *N*-benzyl-β-proline.

Formation of the methyl ester was shown by the comparison of the spectroscopic data to that described previously, highlighted by the introduction of the methyl ester resonance of **324** at δ 3.67 ppm. The ¹³C NMR also revealed that the diastereomers formed by amine protonation no longer remained. Optical rotation of **324** in chloroform gave an $[\alpha]^{23}_{\text{D}}$ of 9.74 ($c = 1.95$), compared to the value for $[\alpha]^{23}_{\text{D}}$ of 19.0 ($c = 1.0$) reported by Gmeiner for **324**. This result confirmed the (*S*) configuration of the stereocentre formed from epimerisation, however it is not clear if some epimerisation occurred during the hydrolysis or esterification steps or if there were slight impurities as the optical rotation was performed on a crude product. Due to time constraints chiral GC analysis was not performed, however this would give a better indication of the optical purity of the sample.

2.7 Spirocyclic Natural Products

A particular class of tricyclic pyrrolidine containing alkaloids of interest to us is the cylindricine class of compounds (**325-329**), originally isolated by Blackman at the University of Tasmania, from the native Tasmanian ascidians *Clavelina cylindrica*, (Figure 16).^{200,201,202}

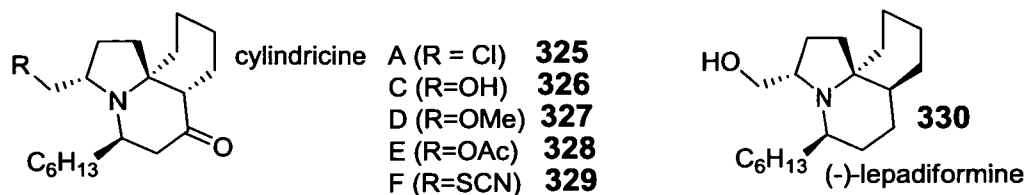
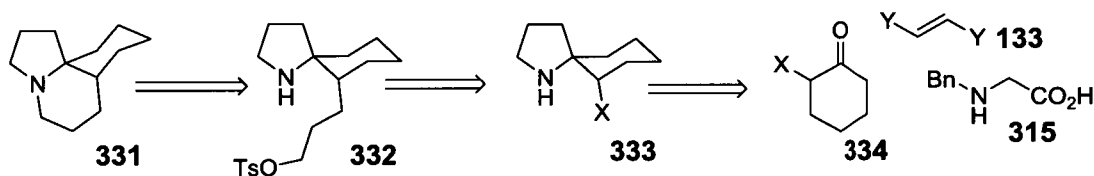


Figure 16: Spirocyclic pyrrolidine containing alkaloids.

Shortly after this first isolation, the group of Biard²⁰³ reported the isolation and elucidation of a related alkaloid named (-)-lepadiformine **330**, which was found in the ascidian *Clavelina lepadiformis* collected in the Mediterranean near Tunisia, and later in *Clavelina moluccensis* near Djibouti.²⁰⁴ Bioactivity studies have shown lepadiformine is moderately cytotoxic towards tumour cells *in vitro*,²⁰⁴ and that it has very active anti-arrhythmic properties *in vitro* and *in vivo*.²⁰⁴

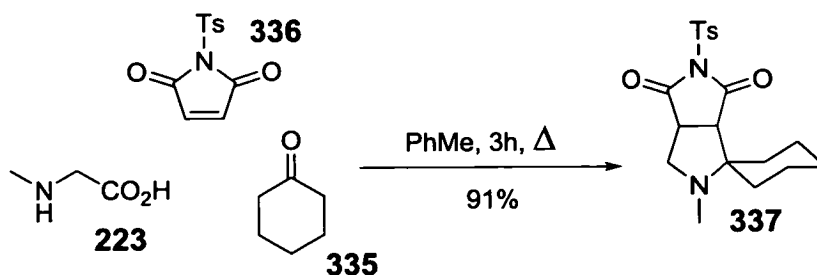
Whilst there are several syntheses of these compounds reported in the literature,²⁰⁵ we aimed to develop an azomethine approach to the decahydro-1H-pyrrolo[1,2-j]quinoline core of these alkaloids. Retrosynthetic analysis of the core structure **331** led to the proposed synthetic plan outlined below, (Scheme 117).



Scheme 117: Retrosynthetic analysis to decahydro-1H-pyrrolo[1,2-j]quinoline core **331**.

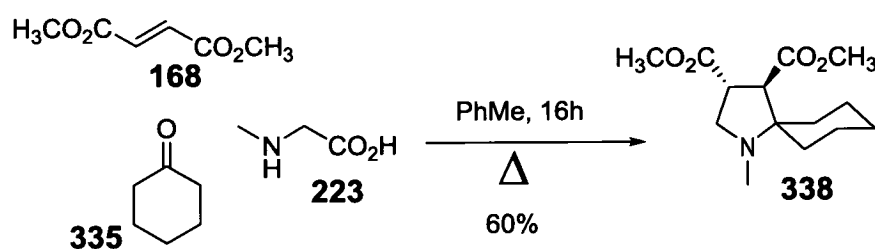
Retrosynthetically, the cylindricine core ring structure **331** could come from a spirocyclic pyrrolidine **332**, utilising the pyrrolidines secondary amine to cyclise onto an appropriately-functionalised side chain. The spirocyclic pyrrolidine **332** could come from elaboration of **333** to allow appropriate chain length for cylindricine formation. Spirocycle **333** could be approached through a three component azomethine ylide coupling reaction featuring a 2-substituted cyclohexanone **334** with *N*-benzylglycine and an ethylene synthon such as the dipolarophile *trans*-1,2-bisphenylsulfonyl ethylene.

Tsuge has provided precedent for the three component couplings through an azomethine route, reporting the cycloaddition between cyclohexanone **335**, sarcosine and the highly reactive *N*-tosylmaleimide **336** to give the bicyclic product **337** in high yield (91%), (Scheme 118).¹⁴²



Scheme 118: Tsuge's spirocyclic cycloaddition.¹⁴²

Thus, as this was the only dipolarophile reported by Tsuge, sarcosine and cyclohexanone were reacted with dimethyl fumarate, phenyl vinyl sulfone and diethyl acetylene dicarboxylate in refluxing toluene, (Scheme 119).



Scheme 119: Investigation to spirocyclic pyrrolidines.

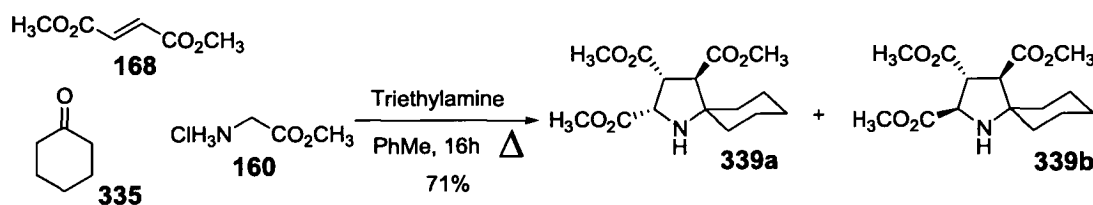
Interestingly, only in the case of dimethyl fumarate was the cycloaddition successful, leading to pyrrolidine **338**. Attempted cycloaddition with phenyl vinyl sulfone led to the Michael adduct being obtained, and reaction with diethyl acetylene dicarboxylate led to unreacted dipolarophile being recovered after work-up.

Formation of cycloadduct **338** was supported by ¹H NMR assignment, with the two methyl ester resonances at δ 3.66 and 3.64 ppm, and the *N*-methyl at δ 2.24 ppm. The four pyrrolidine ring protons were also visible, with a doublet at δ 3.16 ppm, two doublet of

doublets at δ 2.84 and 3.30 ppm and a doublet of doublet of doublets at δ 3.46 ppm. High resolution mass spectroscopy also provided evidence for the formation of **338** with a molecular ion of 269.16253 found. ($C_{14}H_{23}NO_4$ requires 269.16271).

These results indicate dipolarophile choice is limited in these reactions. However, studies continued, and due to the inherent problems of performing an *N*-demethylation, reaction between *N*-benzyl glycine, cyclohexanone and dimethyl fumarate in refluxing toluene was attempted. Unfortunately this did not lead to any observable cycloadduct formation, with unreacted dimethyl fumarate isolated. This indicates that the extra bulk of the *N*-benzyl group, when combined with a carbonyl source that also has extra bulk, such as cyclohexanone, hinders the formation of the iminium ion, the precursor for azomethine ylide formation.

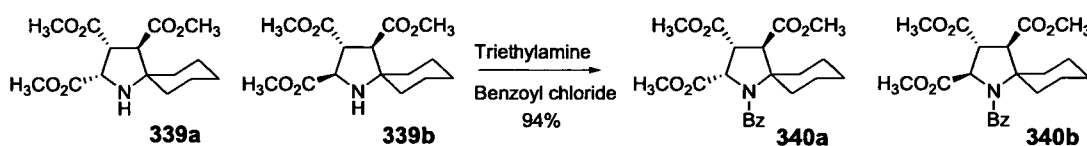
Thus, the primary amine glycine methyl ester, was investigated, as Tsuge had reported thermally-generated stabilised azomethine ylides undergo reaction with maleimide by reflux in toluene, (Scheme 120).¹⁴²



Scheme 120: Amine investigation to spirocyclic pyrrolidines.

In this case diastereomers **339a** and **339b** were obtained in a good yield of 71%, which is in contrast with earlier results using glycine. The major diastereomer **339a** was formed in a 25:1 ratio, and was determined as the major isomer, as the methine proton adjacent to the nitrogen at δ 4.09 ppm was a doublet, with a coupling constant of 8.1 Hz indicative of a *trans* relationship to the neighbouring proton. The methine for the minor diastereomer resonated at δ 4.58 ppm and had a coupling constant of 5.1 Hz.

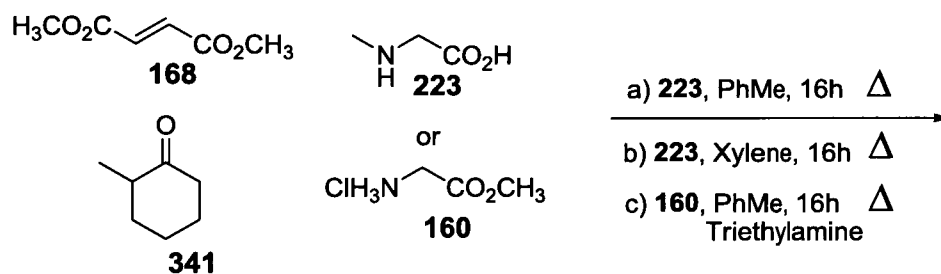
In an attempt to remove the minor diastereomer, the inseparable mixture of **339a** and **339b** was converted into their *N*-benzoyl analogues with the assumption that an amide would be a solid, (Scheme 121).



Scheme 121: Benzoylation of spirocyclic pyrrolidines.

Formation of the *N*-benzoyl derivatives **340a** and **340b** was achieved in 94% yield, however the product, whilst solid, did not crystallise to give solely **340a**. In hindsight a chloro or nitro benzoyl chloride derivative would have been a better choice for recrystallisation, however due to time constraints this was not pursued further.

As a model for synthesis of derivatives that could be elaborated to obtain the target decahydro-1H-pyrrolo[1,2-*j*]quinoline core of lepadiformine and the cylindricine alkaloids, 2-methylcyclohexanone **341** was investigated as the model 2-substituted cyclohexanone, (Scheme 122).



Scheme 122: Attempted 2-methylcyclohexanone cycloadditions.

Attempted decarboxylation or prototropic shift generation of an azomethine ylide from sarcosine or glycine methyl ester and 2-methylcyclohexanone, and cycloaddition with dimethyl fumarate in refluxing toluene or xylene failed in each case. ^1H NMR analysis showed that unreacted 2-methylcyclohexanone was isolated from each reaction, as there were no other doublets below 2 ppm in the ^1H NMR representing the methyl group of the

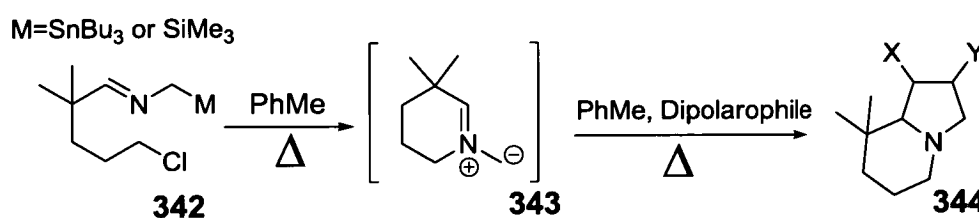
cyclohexane core of cycloadduct. It appears the bulk of the methyl group adjacent to the carbonyl group inhibits formation of the iminium in a similar way as the *N*-benzyl earlier.

Thus, attempts to approach the decahydro-1H-pyrrolo[1,2-*j*]quinoline core were abandoned, although these problems could possibly be overcome by the use of a substrate that could form the ylide intramolecularly.

2.8 Indolizidine synthesis *via* an azomethine route

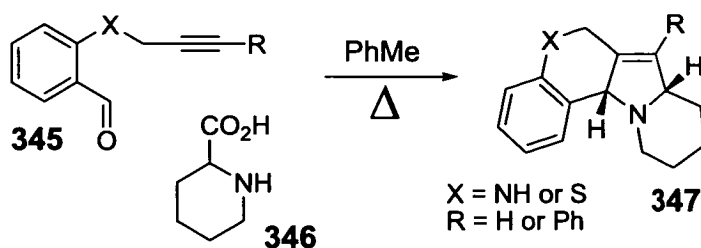
As mentioned in Chapter One, indolizidine alkaloids are a diverse class of naturally-occurring biologically important molecules. Given the results of our investigation into azomethine ylide cycloaddition chemistry for the synthesis of pyrrolidine alkaloids, it was decided to investigate extending this towards the synthesis of indolizidine alkaloids.

Azomethine ylide chemistry has been used previously for the synthesis of various indolizidines. Pearson generated non-stabilised azomethine ylide **343** by the *N*-alkylation of 2-(azaallyl)stannanes and silanes **342**.²⁸ Cycloaddition of **343** with both electron rich and electron poor dipolarophiles, such as acrylates and styrene, yielded a variety of indolizidines **344**, (Scheme 123).²⁸



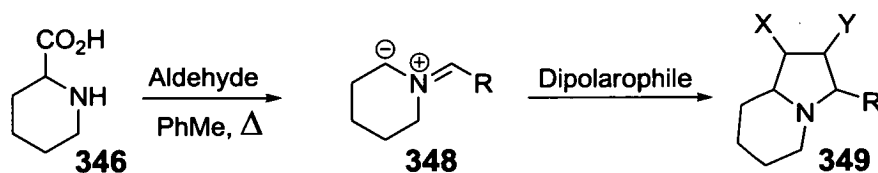
Scheme 123: Pearson's azomethine ylide indolizidine synthesis.²⁸

Bashiardes has also utilised azomethine chemistry to form tetracyclic ring structures containing an indolizidine core **347**.²⁰⁶ He utilised pipecolic acid **346**, the piperidine analogue of proline, to undergo decarboxylative azomethine ylide generation with an aromatic aldehyde **345**, followed by intramolecular trapping with an alkyne, (Scheme 124).



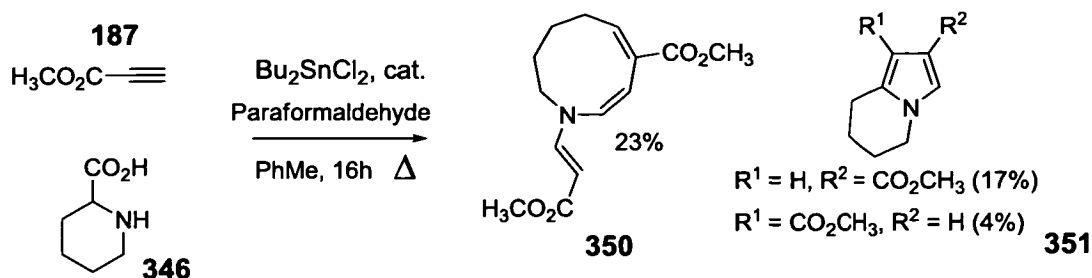
Scheme 124: Bashariades azomethine construction of indolizidine ring.²⁰⁶

We decided to elaborate further the use of pipecolic acid as a cyclic amino acid for the formation of indolizidines, as pioneered by Bashariades. However, instead of utilising a dipolarophile tethered to the aldehyde source, we proposed to investigate the intermolecular reaction targeting a bicyclic system, (Scheme 125).



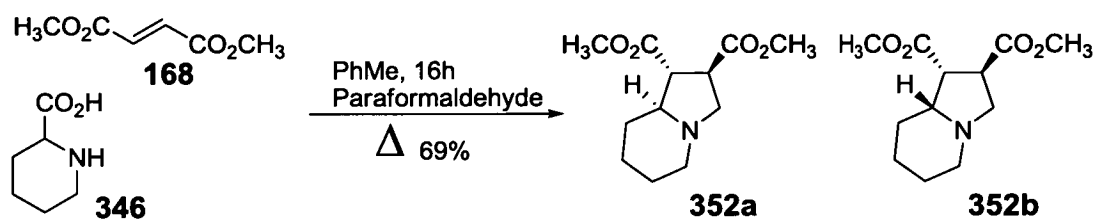
Scheme 125: Proposed indolizidine formation from decarboxylative azomethine cycloaddition.

This would be a very quick method for the construction of an indolizidine skeleton, and allows the introduction of functionality around the 5-membered ring portion of the indolizidine through substitution of the dipolarophile and the azomethine ylide. The only downside to this method is that to introduce functionality into the 6-membered ring portion of the indolizidine, a substituted pipecolic acid would be required. Grigg has reported the use of this method with methyl propiolate as the dipolarophile, however this was found to give a mixture of pyrroles **351**, as well as a ring expanded product **350**, (Scheme 126).²⁰⁷ Thus, we focussed on the use of alkenyl dipolarophiles.



Scheme 126: Grigg's cycloaddition to alkynyl dipolarophile.²⁰⁷

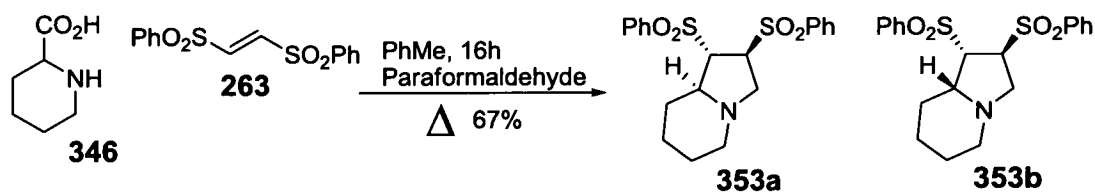
Initial test reaction between dimethyl fumarate, pipecolic acid and paraformaldehyde in refluxing toluene allowed isolation of a 1:1 mixture of inseparable diastereomers **352a** and **352b** in 69% yield, (Scheme 127).



Scheme 127: Indolizidine formation *via* decarboxylative azomethine cycloaddition.

^1H NMR analysis indicated the formation of a 1:1 mixture of **352a** and **352b**, as four distinct methyl ester resonances were observed at δ 3.69, 3.68, 3.67 and 3.66 ppm. The remaining proton resonances were overlapped, however the ^{13}C NMR spectrum had twenty four resonances, including four carbonyl resonances.

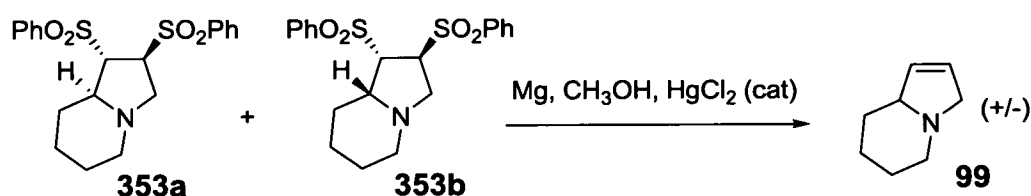
Given the success of the test reaction with the highly active dipolarophile dimethyl fumarate, the indolizidine forming chemistry was extended to the acetylene/ethene equivalent 1,2-*trans*-bisphenylsulfonyl ethylene, (Scheme 128).



Scheme 128: Indolizidine formation with *trans*-1,2-phenylsulfonyl ethylene.

Cycloaddition occurred under the thermal conditions to give a 1:1 mixture of two diastereomers, **353a** and **353b**, in 67% yield, that were partially separable by flash chromatography. Due to the lack of diagnostic peaks in the proton NMR, the two

diastereomers were identified by the 8 aliphatic carbon resonances in the ^{13}C NMR, as well as 8 aromatic carbons. High resolution mass spectroscopy identified a molecular ion of 405.10529, and $\text{C}_{20}\text{H}_{23}\text{NO}_4\text{S}_2$ requires 405.10685. While stereochemical assignment was not possible, it was not required, as treating the mixture of these diastereomers with magnesium in methanol led to desulfonation forming the known highly volatile dehydro-indolizidine **99**, which was isolated as its hydrochloride salt in 76% yield, (Scheme 129). This molecule had been synthesised by us previously,³⁹ as well as by Huxtable,⁶⁹ and was spectrally congruent when synthesised by this method. The elimination of the phenylsulfonyl groups was shown by the absence of aromatic peaks in both the ^1H and ^{13}C NMR spectra. The ^1H NMR also showed the presence of the newly formed alkene with a multiplet integrating for two protons at δ 5.84 ppm.



Scheme 129: Desulfonation of phenylsulfonyl indolizidines **353a** and **353b**.

As mentioned in the previous chapter, synthesis of 2,3-dehydroindolizidine **99** technically represents a total formal synthesis of (\pm)-*epi*-lentignosine **10**,⁶⁹ although Huxtable's conversion of **99** to lentignosine required stoichiometric osmium tetroxide, and was extremely low yielding. However, it does demonstrate the use of this method for the synthesis of an indolizidine core that could be functionalised further.

2.7 Conclusion

The preliminary studies on the application of 1,3-dipolar cycloaddition chemistry of azomethine ylides to the synthesis of pyrrolidine alkaloids showed that development of a common methodology is challenging and the reaction conditions employed depend on the particular dipolarophile and ylide partner. The LiBr mediated reaction between stabilised azomethine ylides and dipolarophiles pioneered by Tsuge, has been improved by the use of higher temperatures that result in shortened reaction times, and by exclusion of base, which was generally found not to be required for efficient transformations, albeit in some cases the higher temperatures resulted in a lower diastereoselectivity.

The use of *trans*-1,2-bisphenylsulfonylethylene as an acetylene equivalent for the reaction with non-stabilised azomethine ylides allowed for the total formal synthesis of (±)-codonopsinine. The reaction of sodium percarbonate and trifluoroacetic acid was an exceptionally convenient method to generate trifluoroperacetic acid, and this powerful reagent allowed the epoxidation of *N*-methyl pyrroline **280**, which was elaborated to the synthesis of *epi*-codonopsinine isomers. Further investigations into the use of *trans*-1,2-bisphenylsulfonylethylene in cycloadditions with azomethine ylides for the generation of 3-pyrrolines should allow for the development of synthetic methods to other alkaloids such as preussin and anisomycin. The expansion of the studies into azomethine ylide reactions of cyclic amino acids should enable extension towards the successful synthesis of a range of bicyclic alkaloids.

Investigations into non-stabilised azomethine ylide chemistry also led to a new highly efficient method for the synthesis of *N*-methyl amino acids being developed.

The use of (-)-8-phenylmenthol as a chiral auxiliary allowed for the asymmetric synthesis of (*S*)-*β*-proline. The auxiliary does not provide efficient stereoselectivity in the cycloaddition reaction; however, in the presence of base this auxiliary allows for selective epimerisation to the required proline form. Further studies into the epimerisation of (-)-8-phenylmenthol

carboxylate substituted pyrrolidines, should lead to this auxiliary being widely adopted as a tool for control of the stereochemistry of pyrrolidine carboxylates.

Chapter 3: Experimental

3.1 General Experimental

Nuclear Magnetic Resonance Spectroscopy:

Proton (^1H) and (^{13}C) nuclear magnetic resonance spectra were recorded in deuterated chloroform (CDCl_3) unless otherwise stated, on a Varian Mercury 2000 Spectrometer operating at 300 MHz and 75 MHz respectively. Chemical shifts were recorded as δ values in parts per million (ppm) and referenced to the solvent used. (In the case of CDCl_3 at 7.26 ppm and 77.16 ppm for ^1H and ^{13}C spectra respectively).²⁰⁸ The following abbreviations are used in assigning ^1H spectra; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; bs = broad singlet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; qdd = quartet of doublet of doublets; at = apparent triplet (no coupling constant given, due to the non-first order coupling observed); J = coupling constant (Hertz).

Infrared Spectroscopy:

Infrared spectra were recorded on a Shimadzu FTIR 8400s spectrometer, using sodium chloride plates. Liquids and solids were recorded as thin films unless stated otherwise.

Chiral Gas Chromatography:

Sample mixtures were analysed using a Hewlett Packard 5890 Series II Gas Chromatograph running a flame ionisation detector loaded with an Agilent Technologies Cyclosil B capillary (30m, 0.25 mm, 0.25 μm) featuring a 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyl dimethylsilyl)- β -cyclodextrin in DB-1701 stationary phase. Oven temperature was 120°C, injector and detector temperatures were 200°C and the head pressure was 20 psi.

Mass Spectrometry:

Mass spectroscopy and Hi-Res mass spectrometry was performed on a Kratos Concept ISQ mass instrument using electron impact mass spectrometry or by LSIMS with *m*-nitrobenzoic acid as the matrix. Alternately a Thermoscientific I.T.Q. Orbitrap using either ESI or APCI

modes was used.

Sample mixtures were analysed using a Varian CP – 3800 Gas Chromatograph loaded with a Varian FactorFour: CC. VF – 5 ms, 0.25mm, 0.25 μ m, column. This fed directly into a Varian 1200 Triple Quadrupole mass spectrometer using which recorded mass spectrum using electron impact mass spectrometry (EI). Analytical analyses were performed by The Central Sciences Laboratory at the University of Tasmania. The molecular ion and mass fragments are quoted, with relative intensities of the peaks referenced to the most intense taken as 100%.

Column Chromatography:

Flash grade Silica Gel (32 - 63 μ m) was used for column and flash chromatography. The general method of Still²⁰⁹ was followed.

Thin Layer Chromatography (TLC):

Merck silica gel 60 F₂₅₄ aluminium backed sheets were used for analytical thin layer chromatography. TLC plates were visualised under 254nm UV lamp and / or by treatment with an alkaline potassium permanganate dip (3 g KMnO₄, 20 g K₂CO₃, 5 mL 5% aqueous NaOH, 300 mL water) or a phosphomolybdic acid (37.5g), ceric sulfate (7.5g), sulfuric acid (37.5ml), water (720ml) dip, followed by heating.

Solvents and Reagents:

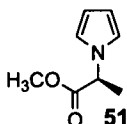
All solvents and reagents were purified by standard laboratory procedures.¹⁵¹ Anhydrous magnesium sulfate was used for drying unless otherwise stated and solvents were removed under reduced pressure on a rotary evaporator. Anhydrous solvents (tetrahydrofuran, diethyl ether, and toluene) were dried using an Innovative Technology SPS400-7 solvent drying machine fitted with activated alumina and copper catalyst columns. Anhydrous dichloromethane was obtained by distillation from calcium hydride. Dimethylsulfoxide (DMSO), dimethylformamide (DMF), and methanol were dried using fresh 4 Å molecular sieves for a minimum of 24 hrs before use.

Optical Rotation:

Optical rotations were recorded using a Rudolph research analytical Autopol III automatic polarimeter.

X-Ray Crystallography:

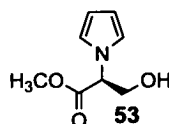
Single crystal x-ray structure determination and structure solution was carried out by Dr. Roderick Jones in the School of Chemistry, University of Tasmania at -80°C using an Enraf-Nonius CAD4 diffractometer with a graphite single crystal monochromated molybdenum radiation source, with λ assumed to be 0.71073 Å (K_{α}). All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions and refined using a riding model with fixed C-H distances of 0.95 Å (sp^2 C-H) and 0.98 Å (CH_3), and $U_{iso}(H) = 1.2U_{eq}(C)$ (sp^2) and $1.5U_{eq}(C)$ (sp^3).

3.2 Chapter 1 Experimental details**(S)-Methyl 2-(1H-pyrrol-1-yl)propanoate (51)**

Under an atmosphere of N_2 a solution of 2,5-dimethoxytetrahydrofuran (200 μ L, 1.544 mmol) was heated under reflux in water (2 mL) for 2 hours. The mixture was allowed to cool to room temperature before the addition of dichloromethane (3.0 mL), sodium acetate (0.304 g, 3.705 mmol), and L-alanine methyl ester hydrochloride (0.165 g, 1.852 mmol). The mixture was then stirred vigorously for 15h with exclusion from light. The reaction mixture was made alkaline with 2M sodium carbonate (5 mL), and the pyrrole extracted with dichloromethane (3 x 5 mL). The organic extracts were dried over magnesium sulfate and filtered through a plug of silica gel with ethyl acetate/hexanes (20:80) and the solution concentrated to yield the pyrrole derivative in 93% yield as a colourless oil.

IR ν_{MAX} :	2954, 1746 (C=O str), 1491, 1436, 1203, 1097, 1053, 1016, 943, 726.
^1H δ :	1.74 (d, J = 7.2 Hz, 3H), 3.73 (s, 3H), 4.79 (q, J = 7.2 Hz, 1H), 6.21 (at, 2H), 6.76 (at, 2H).
^{13}C δ :	18.6 (CH ₃), 52.9 (CH ₃), 57.1 (CH), 108.8 (CH), 119.9 (CH), 172.0 (C=O).

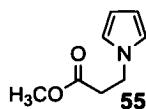
(S)-Methyl 3-hydroxy-2-(1H-pyrrol-1-yl)propanoate (53)



The α -pyrrolic ester **53** was synthesised in 89% yield as per the modified Clauson-Kaas pyrrole synthesis outlined for **51** above.

IR ν_{MAX} :	3445 (OH str), 2956, 1748 (C=O str), 1652, 1558, 1489, 1459, 1282, 1097, 938, 740, 668.
^1H δ :	2.28 (bs, 1H), 3.76 (s, 3H), 4.01- 4.16 (m, 2H), 4.74-4.78 (m, 1H), 6.21 (at, 2H), 6.76 (at, 2H).
^{13}C δ :	53.0 (CH ₃), 63.4 (CH ₂), 63.6 (CH), 109.3 (CH), 120.7 (CH), 170.0 (C=O).

Methyl 3-(1H-pyrrol-1-yl)propanoate (55)



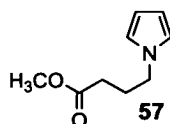
The β -pyrrolic ester **55** was synthesised in 90% yield as per the modified Clauson-Kaas pyrrole synthesis outlined for **51** above. Spectroscopic details were consistent with those reported earlier.⁵⁵

IR ν_{MAX} :	2953, 1732 (C=O str), 1500, 1438, 1366, 1285, 1210, 1168, 1091, 1074, 729.
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^1H δ : 2.78 (t, J = 6.9 Hz, 2H), 3.70 (s, 3H), 4.22 (t, J = 6.9 Hz, 2H), 6.15 (at, 2H), 6.67 (at, 2H).

^{13}C δ : 36.6 (CH_2), 45.1 (CH_2), 52.2 (CH_3), 108.7 (CH), 120.8 (CH) 171.8 (C=O).

Methyl 4-(1H-pyrrol-1-yl) butanoate (**57**)



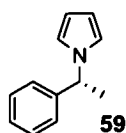
The γ -pyrrolic ester **57** was isolated as a clear oil in 91% yield as per the modified Clauson-Kaas pyrrole synthesis outlined for **50** above. Spectroscopic details were consistent with those reported earlier.⁵⁶

IR ν_{MAX} : 2952, 2360, 1737 (C=O str), 1501, 1437, 1282, 727, 618.

^1H δ : 2.10 (m, 2H), 2.30 (t, J = 6.9 Hz, 2H), 3.70 (s, 3H), 3.96 (t, J = 6.9 Hz, 2H), 6.17 (at, 2H), 6.66 (at, 2H).

^{13}C δ : 27.0 (CH_2), 31.0 (CH_2), 48.7 (CH_2), 51.9 (CH_3), 108.5 (CH), 120.7 (CH), 173.5 (C=O).

(*R*)-1-(1-Phenylethyl)-1H-pyrrole (**59**)



A solution of 2,5-dimethoxytetrahydrofuran (200 μL , 1.544 mmol) was heated under reflux in water (2 mL) for 2 hours. The mixture was allowed to cool to room temperature before the addition of dichloromethane (3.0 mL), sodium acetate (0.152 g, 1.852 mmol), acetic acid (0.106 mL, 1.852 mmol) and (*R*)-phenylethylamine (239 μL , 1.852 mmol). The mixture

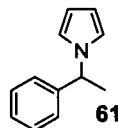
was then stirred vigorously for 15h with exclusion from light. The reaction mixture was made alkaline with 2M sodium carbonate (5 mL), and the pyrrole extracted with dichloromethane (3 x 5 mL). The organic extracts were dried over magnesium sulfate and filtered through a plug of silica gel with ethyl acetate/hexanes (20:80) and the solution concentrated to yield the pyrrole **59** derivative in 91% yield as a colourless oil. Spectroscopic details were consistent with those reported earlier.⁵⁷

IR ν_{MAX} : 634, 699, 1089, 1275, 1449, 1491. 2980.

^1H δ : 1.85 (d, J = 6.9Hz, 3H), 5.29 (q, J = 6.9 Hz, 1H), 6.20 (at, 2H), 6.77 (at, 2H), 7.08 - 7.12 (m, 2H), 7.26 - 7.35 (m, 3H).

^{13}C δ : 22.3 (CH_3), 58.2(CH), 108.1 (CH), 119.6 (CH), 126.0 (CH), 127.6 (CH), 128.8 (CH), (1 aromatic resonance missing or overlapped).

(\pm)-1-(1-Phenylethyl)-1H-pyrrole (**61**)

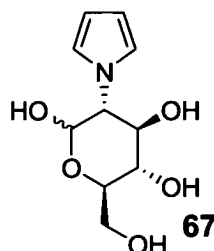


The pyrrole **61** was synthesised in 89% yield as per the modified Clauson-Kaas pyrrole synthesis outlined for **59** above. Spectroscopic details were consistent with those reported earlier.⁵⁷

IR ν_{MAX} : 634, 699, 1089, 1275, 1449, 1491. 2980.

^1H δ : 1.85 (d, J = 6.9Hz, 3H), 5.29 (q, J = 6.9 Hz, 1H), 6.20 (at, 2H), 6.77 (at, 2H), 7.08 - 7.12 (m, 2H), 7.26 - 7.35 (m, 3H).

^{13}C δ : 22.3 (CH_3), 58.2(CH), 108.1 (CH), 119.6 (CH), 126.0 (CH), 127.6 (CH), 128.8 (CH), (1 aromatic resonance missing or overlapped).

(3*R*,4*R*,5*S*,6*R*)-6-(hydroxymethyl)-3-(1*H*-pyrrol-1-yl)tetrahydro-2*H*-pyran-2,4,5-triol (67)

A solution of 2,5-dimethoxytetrahydrofuran (200 μ L, 1.544 mmol) was heated under reflux in water (2 mL) for 2 hours. The mixture was allowed to cool to room temperature, before sodium acetate (0.304 g, 3.705 mmol) and D-glucosamine hydrochloride (0.399 g, 1.544 mmol) were added. The mixture was then stirred vigorously for 15h with exclusion from light. The reaction mixture was condensed *in vacuo*, and purified by short path chromatography with methanol/dichloromethane (20:80). The appropriate fractions were concentrated to yield the pyrrole **67** as a colourless gummy residue in 88% yield as a 2:1 mixture of anomers. Spectroscopic details were consistent with those reported earlier.⁵⁸

Anomer 1 (Major):

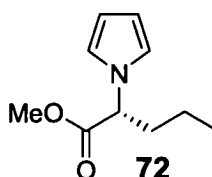
^1H D_2O δ : 3.46 – 3.84 (m, 4H), 3.91 (dd, $J_1 = 11.6$ Hz, $J_2 = 2.3$ Hz, 1H), 3.97 (dd, $J_1 = 11.6$ Hz, $J_2 = 8.8$ Hz, 1H), 5.06 (d, $J = 8.4$ Hz, 1H), 6.21 (at, 2H), 6.88 (at, 2H).

^{13}C D_2O δ : 60.81, 66.27, 70.08, 74.37, 76.09, 94.99, 108.61, 120.37.

Anomer 2 (Minor):

^1H δ (D_2O): 3.46 – 3.84 (m, 4H), 4.08 (dd, $J_1 = 11\text{Hz}$, $J_2 = 3.3$ Hz, 1H), 4.22 (dd, $J_1 = 11\text{Hz}$, $J_2 = 8.7$ Hz, 1H), 5.28 (d, $J = 3.4$ Hz, 1H), 6.19 (at, 2H), 6.93 (at, 2H).

^{13}C δ (D_2O): 60.66, 63.30, 70.50, 70.58, 71.69, 92.46, 108.13, 121.17.

(*R*)-Methyl 2-(1*H*-pyrrol-1-yl)pentanoate (72)

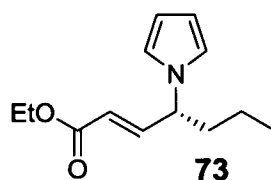
The α -pyrrolic ester **72** was synthesised in 94% yield as per the modified Clauson-Kaas pyrrole synthesis outlined for **51** above.

IR ν_{MAX} : 2958, 2832, 1744 (C=O str), 1440, 1368, 1200, 1273, 1228, 1102, 830, 755, 728.

^1H δ : 0.94 (t, J = 7.5 Hz, 3H), 1.26 (m, 2H), 2.05 (m, 2H), 3.73 (s, 3H), 4.60 (dd, J_1 = 9.3 Hz, J_2 = 6.3 Hz, 1H), 6.19 (at, 2H), 6.76 (at, 2H).

^{13}C δ : 13.4 (CH_3), 19.0 (CH_2), 34.7 (CH_2), 52.3 (CH_3), 61.5 (CH), 108.4 (CH), 119.9 (CH), 171.3 (C=O).

(*R,E*)-Ethyl 4-(1H-pyrrol-1-yl)hept-2-enoate (73**)**



A solution of (*R*)-methyl 2-(1H-pyrrol-1-yl)pentanoate **72** (0.528 g, 2.914 mmol) in anhydrous dichloromethane (80 mL) under an atmosphere of nitrogen was cooled to -78°C . Diisobutyl aluminium hydride (DIBAL-H) (2.331 mL of a 1.5 M solution in toluene, 3.497 mmol) was then added to the reaction mixture drop-wise and the reaction stirred at this temperature for 45 min. In a separate flask triethyl phosphonoacetate (0.723 mL, 3.642 mmol) was added drop-wise to a suspension of sodium hydride (0.160 g, 4.01 mmol) in anhydrous tetrahydrofuran (THF) (25 mL) under nitrogen at 0°C . The solution was cooled to -78°C before transfer by cannular to the first reaction mixture. Stirring at -78°C was continued for a further 30 min, then warmed to room temperature and stirred for a further 15 h. The reaction mixture was quenched with water (1 mL) then evaporated to dryness. Water (20 mL) was then added followed by 0.5 M potassium hydrogen sulfate until the solution was acidic (10 mL) and the aqueous solution extracted with dichloromethane (3 x

20 mL). The combined extracts were dried and the solvent removed to give the crude product. The product was purified by silica gel chromatography by elution with 10% ethyl acetate-hexanes. The product **73** was isolated as a yellow oil in 70% yield (449 mg).

IR: 2961, 2935, 1721, 1658, 1488, 1368, 1310, 1272, 1179, 725, 631.

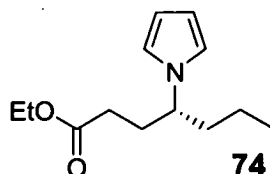
MS (EI) m/z : 221(35%, M^+) 176 (20), 148(100), 106(60), 67(20).

HRMS-EI m/z : 221.1414 $[M]^+$ calcd for $C_{13}H_{19}NO_2$: 221.1415.

1H δ : 0.93 (t, J = 7.2 Hz, 3H), 1.27 (m, 5H), 1.90 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.58 (m, 1H), 5.63 (dd, J_1 = 15.6 Hz, J_2 = 1.8 Hz, 1H), 6.18 (at, 2H), 6.67 (at, 2H), 7.02 (dd, J_1 = 15.6 Hz, J_2 = 5.7 Hz, 1H).

^{13}C δ : 13.6 (CH₃), 14.2 (CH₃), 19.3 (CH₂), 36.6 (CH₂), 60.0 (CH₂), 60.1 (CH), 108.4 (CH), 119.2 (CH), 121.6 (CH), 147.7 (CH), 166.2 (C=O).

(*R*)-Ethyl 4-(1H-pyrrol-1-yl)heptanoate (**74**)



(*R,E*)-Ethyl 4-(1H-pyrrol-1-yl)hept-2-enoate (0.385 g, 1.74 mmol) was hydrogenated with 10% Pd/C (18 mg) under 40 PSI of H₂ in a Parr shaker hydrogenator for 3h.

Filtration through a bed of celite, followed by concentration *in vacuo* gave (*R*)-ethyl 4-(1H-pyrrol-1-yl)heptanoate as a clear oil in 91% yield (0.353 g).

IR: 2959, 2934, 1733, 1490, 1376, 1274, 1257, 1178, 1089, 724, 639.

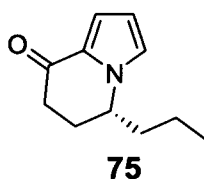
MS (EI) m/z : 223(40%, M^+) 178 (30), 122(50), 106(30), 94(60), 87(50), 47(40).

HRMS-EI m/z : 223.1571 $[M]^+$ calcd for $C_{13}H_{21}NO_2$: 223.15723

^1H δ : 0.87 (t, J = 7.2 Hz, 3H), 1.22 (m, 5H), 1.70 (m, 2H), 1.98 (m, 2H), 2.09 (m, 2H), 3.84 (m, 1H), 4.09 (q, J = 6.9 Hz, 2H), 6.13 (at, 2H), 6.62 (at, 2H).

^{13}C δ : 13.7 (CH_3), 14.2 (CH_3), 19.4 (CH_2), 30.7 (CH_2), 31.6 (CH_2), 38.7 (CH_2), 59.2 (CH), 60.3 (CH_2), 107.7 (CH), 118.8 (CH), 173.1 (C=O).

(*R*)-5-Propyl-6,7-dihydroindolizin-8(5H)-one (75)



Boron tribromide (0.906 mL, 0.9731 M, 0.842 mmol) was added dropwise to a stirred solution of (*R*)-ethyl 4-(1H-pyrrol-1-yl)heptanoate (0.179 g, 0.802 mmol) in anhydrous dichloromethane (20 mL) under nitrogen at 0°C. The solution was stirred at this temperature for 10 min and was then quenched by the careful addition of water (10 mL) and 2 M sodium carbonate (10 mL). The organic layer was separated and the aqueous extracted with dichloromethane (2 x 20 mL). The combined organic extracts were then dried and filtered through silica gel with ethyl acetate as an eluent. The filtrate was then concentrated to yield the bicyclic product **75** as a colourless solid in 89% yield, mp = 52-53 °C.

IR: 2959, 2934, 2360, 1660, 1530, 1464, 1410, 1393, 1331, 1072, 1056, 747, 616.

MS (EI) m/z : 177(80%, M^+) 149 (60), 134 (100), 106(90), 93(80), 87(35), 47(50).

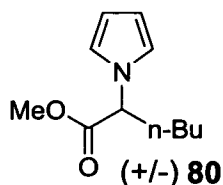
HRMS-EI m/z : 177.1151 [M] $^+$ calcd for $\text{C}_{11}\text{H}_{15}\text{NO}$: 177.1152.

^1H δ : 0.95 (t, J = 7.2 Hz, 3H), 1.41 (m, 2H), 1.73 (m, 1H), 1.86 (m, 1H), 2.07 (m, 1H), 2.33 (m, 1H), 2.47 (m, 1H), 2.65 (m, 1H), 4.15 (m, 1H), 6.21 (dd, J_1 =

3.9 Hz, $J_2 = 2.4$ Hz, 1H), 6.90 (at, 1H), 6.98 (dd, $J_1 = 3.9$ Hz, $J_2 = 1.5$ Hz, 1H).

^{13}C δ : 13.8 (CH_3), 19.2 (CH_2), 27.6 (CH_2), 33.1 (CH_2), 36.3 (CH_2), 54.5 (CH), 110.0 (CH), 114.1 (CH), 125.0 (CH), 130.1 (C), 187.1 (C=O).

(\pm)-Methyl 2-(1H-pyrrol-1-yl)hexanoate (80**)**



The α -pyrrolic ester **80** was synthesised in >95% yield from DL-norleucine methyl ester hydrochloride **79** (3.123 g, 17.19 mmol) as per the modified Clauson-Kaas pyrrole synthesis outlined for **51** above.

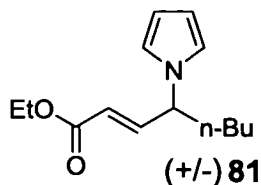
IR: 2957, 2863, 1747, 1489, 1438, 1278, 1173, 1092, 1024, 726, 619.

MS (EI) m/z : 195(25%, M^+) 136 (100), 107 (20), 134(75), 87(30), 80(50), 47(40).

HRMS-EI m/z : 195.1260 [M] $^+$ calcd for $\text{C}_{11}\text{H}_{17}\text{NO}_2$: 195.1259.

^1H δ : 0.88 (t, $J = 6.9$ Hz, 3H), 1.18 – 1.28 (m, 4H), 2.00 – 2.16 (m, 2H), 3.72 (s, 3H), 4.55 (dd, $J_1 = 9.6$ Hz, $J_2 = 6$ Hz, 1H), 6.18 (at, 2H), 6.75 (at, 2H).

^{13}C δ : 13.9 (CH_3), 22.2 (CH_2), 28.0 (CH_2), 32.6 (CH_2), 52.5 (CH_3), 62.0 (CH), 108.6 (CH), 120.1 (CH), 171.6 (C=O).

(±)-(E)-Ethyl 4-(1H-pyrrol-1-yl)oct-2-enoate (81**)**

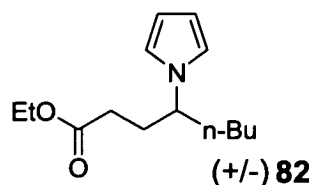
The same procedure as for the synthesis of **73** was followed to give (±)-(E)-ethyl 4-(1H-pyrrol-1-yl)oct-2-enoate as a clear oil from **80** (2.00 g, 10.24 mmol) in 41% yield (0.994 g).

MS (EI) m/z : 235(40%, M^+) 190 (20), 162(70), 106(80), 94(45), 87(70), 80 (60), 67 (50), 47(100).

HRMS-EI m/z : 235.1570 [M] $^+$ calcd for $C_{14}H_{21}NO_2$: 235.1571.

1H δ : 0.88 (t, J = 6.9 Hz, 3H), 1.20 – 1.38 (m, 7H), 1.86 – 1.94 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.54 – 4.61 (m, 1H), 5.64 (dd, J_1 = 15.6 Hz, J_2 = 1.8 Hz, 1H), 6.19 (at, 2H), 6.68 (at, 2H), 7.03 (dd, J_1 = 15.6 Hz, J_2 = 5.4 Hz, 1H).

^{13}C δ : 13.9 (CH_3), 14.3 (CH_3), 22.3 (CH_2), 28.3 (CH_2), 34.3 (CH_2), 60.4 (CH_2), 60.6 (CH), 108.4 (CH), 119.2 (CH), 121.7 (CH), 147.8 (CH), 166.2 (C=O).

(±)-Ethyl 4-(1H-pyrrol-1-yl)octanoate (82**)**

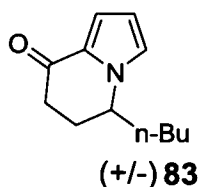
The α,β -unsaturated ester **81** (0.913 g, 3.88 mmol) was hydrogenated as per **73** to give (±)-ethyl 4-(1H-pyrrol-1-yl)octanoate **82** as a clear oil in >95% yield (0.920 g).

IR: 2958, 2863, 1715, 1488, 1368, 724, 632 cm^{-1} .

^1H δ : 0.84 (t, J = 7.2 Hz, 3H), 1.20 – 1.30 (m, 7H), 1.68 – 1.78 (m, 2H), 1.92 – 2.00 (m, 2H), 2.04 – 2.12 (m, 2H), 3.72 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 6.13 (at, 2H), 6.62 (at, 2H).

^{13}C δ : 14.1 (CH_3), 14.4 (CH_3), 22.6 (CH_2), 28.6 (CH_2), 31.0 (CH_2), 31.9 (CH_2), 36.6 (CH_2), 59.8 (CH), 60.6 (CH_2), 108.0 (CH), 119.0 (CH), 173.4 (C=O).

(\pm)-5-Butyl-6,7-dihydroindolizidin-8(5H)-one (83**)**



The γ -pyrrolic ester **82** (0.491 g, 2.07 mmol) was cyclised under the same conditions as compound **74** to yield the bicyclic product **83** as a pale yellow oil in >95% yield (0.394 g).

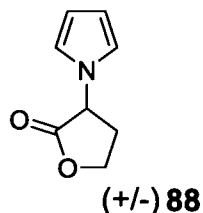
IR: 2930, 2870, 1667, 1531, 1470, 1392, 1072, 736, 616.

MS (EI) m/z : 191(30%, M^+) 163 (50), 148 (30), 134(75), 106(70), 93(60), 87(70), 47(100).

HR-EI-MS m/z : 191.1313 [M] $^+$ calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$: 191.1310.

^1H δ : 0.92 (t, J = 6.6 Hz, 3H), 1.34 – 1.42 (m, 4H), 1.72 – 1.94 (m, 2H), 2.08 – 2.16 (m, 1H), 2.32 – 2.40 (m, 1H), 2.47 – 2.56 (m, 1H), 2.63 – 2.72 (m, 1H), 4.14 – 4.20 (m, 1H), 6.24 (dd, J_1 = 4.2 Hz, J_2 = 2.4 Hz, 1H), 6.92 (m, 1H), 7.02 (dd, J_1 = 4.2 Hz, J_2 = 1.5 Hz, 1H).

^{13}C δ : 14.1 (CH_3), 22.7 (CH_2), 27.8 (CH_2), 28.3 (CH_2), 33.3 (CH_2), 34.1 (CH_2), 54.9 (CH), 110.3 (CH), 114.5 (CH), 125.3 (CH), 130.4 (C), 187.4 (C=O).

(±)-3-(1*H*-Pyrrol-1-yl)-dihydrofuran-2(3*H*)-one (88)

2,5-Dimethoxytetrahydrofuran (5.00 mL, 38.59 mmol), was added to a stirred solution of water (30 mL) and the solution was heated under reflux for 2h under nitrogen. The mixture was allowed to cool to room temperature, before addition of dichloromethane (30 mL), sodium acetate (9.50 g, 115.77 mmol) and homoserine hydrochloride (5.309 g, 38.59 mmol). The reaction mixture was then vigorously stirred for 15h with exclusion from light. The reaction mixture was then made basic with 2M sodium carbonate (15 mL), and the aqueous extracted with dichloromethane (3 x 15 mL). The organic extracts were dried over magnesium sulfate and filtered through a plug of silica gel with 20% ethyl acetate / 80% hexanes as an eluent and concentrated to yield (±)-3-(1*H*-pyrrol-1-yl)-dihydrofuran-2(3*H*)-one in 65% yield (3.81 g) as a white solid. (Mp = 72-74 °C.)

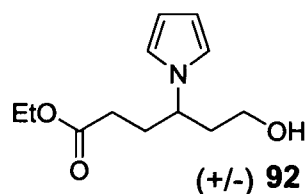
IR: 1781, 1496, 1456, 1292, 1183, 1099, 1022, 1007, 737, 620.

MS (EI) *m/z*: 151(100%, M⁺) 106 (95), 93 (80), 80(30), 67(30), 39(40).

HRMS-EI *m/z*: 151.0635 [M]⁺ calcd for C₈H₉NO₂: 151.0634.

¹H δ: 2.53 – 2.63 (m, 1H), 2.73 – 2.82 (m, 1H), 4.27 – 4.36 (m, 1H), 4.54 – 4.52 (m, 1H), 4.87 (dd, *J*₁ = 11.4 Hz, *J*₂ = 8.7 Hz, 1H), 6.24 (at, 2H), 6.73 (at, 2H).

¹³C δ: 30.7 (CH₂), 56.9 (CH), 65.4 (CH₂), 109.6 (CH), 119.9 (CH), 173.4 (C=O).

(±)-Ethyl 6-hydroxy-4-(1*H*-pyrrol-1-yl)hexanoate (92)

3-(1*H*-Pyrrol-1-yl)-dihydrofuran-2(3*H*)-one **88** (0.180 g, 1.191 mmol) was chain homologated by the general procedure to give the crude alkene **91** which was immediately hydrogenated to yield the alcohol **92** in 54% yield (0.146 g). The compound was immediately taken through the next step without further purification.

IR: 3440, 2934, 1732, 1489, 1446, 1092, 1041, 728, 641.

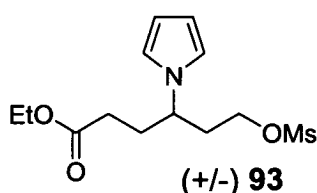
MS (EI) *m/z*: 225(30%, M^+) 181 (50), 153 (20), 106(60), 94(100), 81(70), 67(70), 41 (60).

HRMS-EI *m/z*: 225.1364 [M]⁺ calcd for C₁₂H₁₉NO₃: 225.1364.

¹H δ: 1.22 (t, *J* = 7.2 Hz, 3H), 1.80 (bs, 1H), 1.94 – 2.14 (m, 6H), 3.30 - 3.38 (m, 1H), 3.48 - 3.56 (m, 1H), 4.02 - 4.12 (m, 3H), 6.13 (apparent t, 2H), 6.65 (apparent t, 2H).

¹³C δ: 14.2 (CH₃), 30.7 (CH₂), 31.5 (CH₂), 39.0 (CH₂), 56.1 (CH), 59.2 (CH₂), 60.6 (CH₂), 108.2 (CH), 119.0 (CH), 173.3 (C=O).

(±)-Ethyl 6-(methylsulfonyloxy)-4-(1*H*-pyrrol-1-yl)hexanoate (93**)**

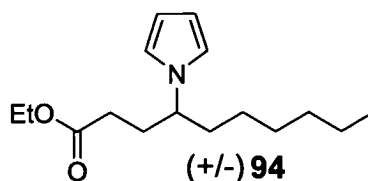


A solution of alcohol **92** (0.146 g, 0.65 mmol) in CH₂Cl₂ (5 mL) was treated with methanesulfonyl chloride (0.081 g, 0.71 mmol) and triethylamine (0.072 g, 0.71 mmol) at 0 °C and stirred for 1h. After stirring it was washed with saturated sodium bicarbonate (5 mL) then 1M HCl (5 mL). Column chromatography with 1:1 ethyl acetate/hexanes yielded the mesylate as a pale yellow oil in 45% yield (0.90 g).

¹H δ: 1.20 (t, *J* = 7.2 Hz, 3H), 2.02 – 2.26 (m, 6H), 2.89 (s, 3H), 3.78 (td, *J*₁ = 9.6 Hz, *J*₂ = 4.5 Hz, 1H), 4.03 – 4.14 (m, 4H), 6.13 (at, 2H), 6.62 (at, 2H).

^{13}C δ : 14.2 (CH_3), 30.5 (CH_2), 31.4 (CH_2), 35.9 (CH_2), 37.1 (CH_3), 55.4 (CH), 60.6 (CH_2), 66.7 (CH_2), 108.7 (CH), 118.9 (CH), 172.8 (C=O).

(\pm)-Ethyl 4-(1H-pyrrol-1-yl)decanoate (94**)**



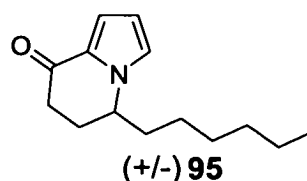
A solution of CuI (0.186 g, 0.98 mmol) in diethyl ether (20 mL) at -20°C was treated with 2M *n*-butyl lithium (0.978 mL, 1.96 mmol). This solution was cooled to -60°C then a solution of the mesylate **93** (0.074 g, 0.24 mmol) in ether was added. The reaction was stirred for 2.5 h before warming to room temperature. The reaction was quenched by addition of saturated NH_4Cl solution (10 mL), and extracted with ether (3 x 10 mL) and concentrated by rotary evaporation. Column chromatography with 20% to 50% ethyl acetate in hexanes yielded the product **94** as a pale yellow oil in 46% yield (0.030 g).

IR: 2928, 2856, 1732, 1488, 1416, 1267, 1092, 1030, 727, 639.

^1H δ : 0.85 (t, $J = 6.9$ Hz, 3H), 1.18 – 1.28 (m, 11H), 1.66 – 1.77 (m, 2H), 1.92 – 2.11 (m, 4H), 3.76 – 3.88 (m, 1H), 4.09 (q, $J = 6.9$ Hz, 2H), 6.13 (at, 2H), 6.62 (at, 2H).

^{13}C δ : 14.2 (CH_3), 14.3 (CH_3), 22.7 (CH_2), 26.3 (CH_2), 29.1 (CH_2), 30.9 (CH_2), 31.8 (CH_2), 31.8 (CH_2), 36.8 (CH_2), 59.7 (CH), 60.5 (CH_2), 107.9 (CH), 118.9 (CH), 173.3 (C=O).

5-Hexyl-6,7-dihydroindolizidin-8(5H)-one (95**)**



The γ -pyrrolic ester **94** was cyclised under the same conditions as compound **74** to yield the bicyclic product **95** as a pale yellow oil in 90% yield.

IR: 1662 (C=O).

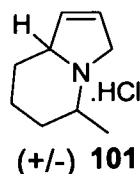
MS (EI) m/z : 219(30%, M^+), 191(20), 148(65), 134(95), 106(100), 93(60), 67(30).

HRMS-EI m/z : 219.1617 [M] $^+$ calcd for $C_{14}H_{21}NO$: 219.1622.

1H δ : 1.51 (d, J = 6.3 Hz, 3H), 1.69 - 1.83 (m, 8H), 1.84 - 1.97 (m, 1H), 2.06 - 2.16 (m, 1H), 2.30-2.42 (m, 1H), 2.51 (ddd, J = 17.7, 9.3, 4.3 Hz, 1H), 2.67 (ddd, J_1 = 17.7 Hz, J_2 10.2 Hz, J_3 4.3 Hz, 1H), 4.15 (m, 1H), 6.24 (dd, J_1 = 3.9 Hz, J_2 = 2.4 Hz, 1H), 6.91 (m, 1H), 7.01 (dd, J_1 = 3.9 Hz, J_2 = 1.5 Hz, 1H);

^{13}C δ : 14.0, 22.5, 26.0, 27.7, 29.1, 31.6, 33.3, 34.3, 54.8, 110.1, 114.3, 125.0, 130.2, 187.2.

5-Methyl-3,5,6,7,8,8a-hexahydroindolizidine hydrochloride (**101**)



Two diastereomers

A stirred solution of 5-methyl-8-oxo-5,6,7,8-dihydroindolizidine **100** (0.100 g, 0.670 mmol) obtained from previous studies,⁴⁸ in methanol (3 mL) was heated to reflux, then removed from the heat and powdered zinc (0.438 g, 6.70 mmol) and 3 mL of 10 M hydrochloric acid were added in small alternating portions to the reaction mixture over ~10 min. After addition the reaction mixture was made alkaline with conc. ammonia (10 mL) and extracted with dichloromethane (3 x 10 mL). The dichloromethane extracts were combined and 10 M hydrochloric acid (2 drops) added. The reaction mixture was

stirred for 15 h then evaporated under reduced pressure to yield the hydrochloride salt **101** (quantitative).

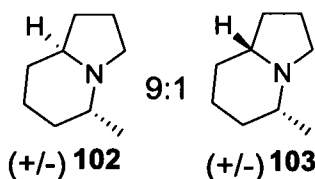
Major Diastereomer:

IR: 3400, 2947, 2604, 2499, 1641, 1474, 1444, 1397, 1037, 807, 704.

^1H δ : 1.42 (d, $J = 6.3$ Hz, 3H), 1.64 (m, 4H), 1.92 (m, 2H), 3.15 (m, 1H), 3.74 (m, 1H), 4.23 (m, 1H), 4.42 (m, 1H), 5.78 (m, 2H), 11.4 (bs, 1H).

^{13}C δ : 16.7, 17.4, 24.3, 27.3, 55.1, 57.4, 65.0, 124.3, 129.9.

(\pm)-(5*R*, 8*aS*) and (5*R*, 8*aR*)-5-Methyloctahydroindolizidine (102**, **103**)**



A mixture of alkene hydrochloride **101** (0.056 g, 0.322 mmol) and 10% Pd/C (20 mg) and 2M HCl (0.1 mL) in ethanol (5 mL) were shaken vigorously under an atmosphere of hydrogen at 40 psi on a Parr shaker hydrogenator for 2 h. The hydrogenation mixture was filtered through Celite™, the filtrate evaporated to dryness and 2M sodium bicarbonate (5 mL) added. The solution was extracted with dichloromethane (3 x 10 mL), the combined extracts were dried and concentrated to yield 5-methyloctahydroindolizidine **102**, **103** (41 mg, 92%) as a 9:1 mixture of *trans/cis* diastereomers. The spectral data are consistent with that previously reported.⁷⁷

Major isomer **102**:

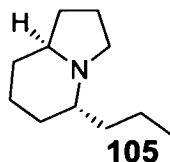
^1H δ : 0.99 (d, $J = 6.6$ Hz, 3H), 1.84 - 1.16 (m, 10H), 2.46 - 2.54 (m, 1H), 2.58 (q, $J = 8.1$ Hz, 1H), 2.84 (td, $J_1 = 9.3$ Hz, $J_2 = 3.0$ Hz, 1H), 3.22 (m, 1H).

^{13}C δ : 10.4, 19.0, 20.7, 30.1, 30.9, 31.1, 49.1, 50.2, 54.9.

Minor isomer **103**:

^{13}C δ : 20.3, 21.0, 24.7, 30.5, (31.1 obscured), 34.2, 51.7, 58.2, 64.8.

epi-Indolizidine 167B ((5*R*, 8*aS*)-5-propyloctahydroindolizine) (**105**)



A stirred solution of (5*R*)-propyl-5,6,7,8-dihydroindolizine **75** (57 mg, 0.322 mmol) in methanol (3 mL) was heated to reflux, then removed from the heat and powdered zinc (0.21 g, 3.22 mmol) and 10 M hydrochloric acid (2 mL) were added in small alternating portions to the reaction mixture over ~ 10 min. After the addition was complete the reaction mixture was made alkaline by addition of conc. ammonia (10 mL) and extracted with dichloromethane (3 x 10 mL). The dichloromethane extracts were combined and 10 M hydrochloric acid (2 drops) was added. The reaction mixture was then evaporated under reduced pressure to yield the hydrochloride salt **104**. A mixture of the crude hydrochloride **104**, 10% Pd/C (20 mg) and 2M HCl (0.1 mL) in ethanol (5mL) was shaken under an atmosphere of hydrogen at 40 psi on a Parr shaker hydrogenator for 2 h. The hydrogenation mixture was filtered through Celite™, evaporated to dryness and 2M sodium bicarbonate (5 mL) added. The solution was extracted with dichloromethane (3 x 10 mL), the combined extracts dried and concentrated to yield **105** and **4** as a clear oil (49 mg, 91%) as a 9:1 mixture of *trans/cis* diastereomers. The spectral data are consistent with that previously reported.^{77,59}

Major isomer *trans*-**105**:

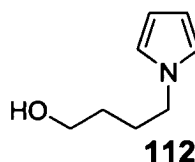
^1H δ : 0.88 (t, J = 7.2Hz, 3H), 1.10 – 1.82 (m, 14H), 2.47 (m, 1H), 2.64 (q, J = 7.8, 1H), 2.91 (m, 1H), 2.82 (td, J_1 = 8.7 Hz, J_2 = 3.0 Hz, 1H),

^{13}C δ : 14.4, 19.2, 20.7, 20.8, 25.9, 27.4, 30.4, 30.9, 48.7, 55.30, 55.33.

Minor isomer *cis*-4:

^{13}C δ : 14.5, 19.1, 20.4, 24.7, 30.5, 30.8, (31.1 obscured), 36.8, 51.5, 63.7, 65.0.

4-(1H-Pyrrol-1-yl)butan-1-ol (**112**)



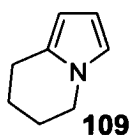
A solution of methyl 4-(1*H*-pyrrol-1-yl) butanoate (**56**) (0.056 g, 0.335 mmol) was dissolved in dry THF (5 mL) and lithium aluminium hydride (0.019 g, 0.502 mmol) was added. The reaction was stirred for 1h, before ethanol (2 mL) was added, followed by saturated potassium hydrogen sulfate solution (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo* to yield 47 mg of **112**, (>95%).

The NMR data was congruent with that reported by Muchowski.⁴⁶

^1H δ : 1.48 – 1.60 (m, 2H), 1.80 – 1.92 (m, 2H), 1.95 (bs, 1H), 3.62 (t, J = 6.7 Hz, 2H), 3.92 (t, J = 6.7 Hz, 2H), 6.15 (apparent t, 2H), 6.67 (apparent t, 2H).

^{13}C δ : 27.99, 29.82, 49.42, 62.32, 107.99, 120.55.

5,6,7,8-Tetrahydroindolizine (**109**)



To a solution of 4-(1*H*-pyrrol-1-yl)butan-1-ol (0.037 g, 0.267 mmol) in CH_2Cl_2 (3 mL) was added triflic anhydride (0.045 mL, 0.267 mmol) and triethylamine (0.037 mL, 0.267 mmol).

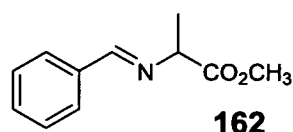
The reaction was stirred for 3h before saturated sodium bicarbonate was added (5 mL) and the mixture separated, and the aqueous extracted with CH_2Cl_2 (2 x 5 mL). The organic extracts were combined, dried (MgSO_4) and concentrated under reduced pressure to yield 31 mg of **109** (>95%).

The ^1H NMR was consistent with that reported previously by Albonico.⁷⁹

^1H δ : 1.77 – 1.97 (m, 4H), 2.78 (t, J = 6.3 Hz, 2H), 3.94 (t, J = 6.3 Hz, 2H), 5.79 – 5.87 (m, 1H), 6.10 – 6.13 (m, 1H), 6.48 – 6.56 (m, 1H).

3.3 Chapter 2 Experimental details

(*E*)-Methyl 2-(benzylideneamino)propanoate (**162**)

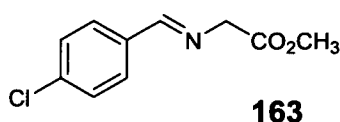


Imine **162** was prepared by the method reported by Tsuge.¹²⁷

Benzaldehyde (0.774 mL, 7.60 mmol) and DL-alanine hydrochloride (1.060 g, 7.60 mmol) were suspended in toluene (8 mL) and triethylamine (1.059 mL, 7.60 mmol) was added. The mixture was heated under Dean – Stark conditions for 16h, before being cooled. Further toluene was added (5 mL) and the mixture washed with water (3 x 5 mL) and dried (MgSO₄). Concentration *in vacuo* yielded a white solid which was purified by trituration with *t*-butyl methyl ether to give 1.39g of **162** (>95%). The product was spectroscopically congruent to that reported by Tsuge.¹²⁷

¹H δ: 1.53 (d, *J* = 6.9 Hz, 3H), 3.75 (s, 3H), 4.17 (q, *J* = 6.9 Hz, 1H), 7.36 – 7.51 (m, 3H), 7.73 – 7.83 (m, 2H), 8.31 (s, 1H).

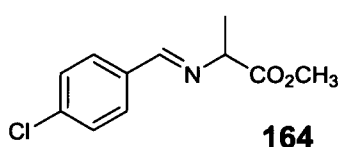
(*E*)-Methyl 2-(4-chlorobenzylideneamino)acetate (**163**)



The imine **163** was synthesised from glycine methyl ester hydrochloride (1.63 g, 13.01 mmol) and *para*-chlorobenzaldehyde (1.83 g, 13.01 mmol) in a quantitative yield by the procedure described above. The product was spectroscopically congruent to the data reported by Wang.¹³¹

IR:	823, 1014, 1088, 1179, 1202, 1271, 1436, 1486, 1595, 1645, 1743 (C=O), 2952.
^1H δ :	3.754 (s, 3H), 4.386 (s, 2H), 7.367 (d, J = 8.4 Hz, 2H), 7.691 (d, J = 8.4 Hz, 2H), 8.224 (s, 1H).
^{13}C δ :	52.225 (CH ₃), 61.845 (CH ₂), 128.974 (CH), 129.726 (CH), 134.054 (C), 137.311 (C), 164.130 (CH), 170.447 (C=O).

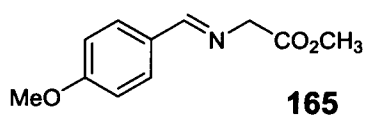
(*E*)-Methyl 2-(4-chlorobenzylideneamino)propanoate (164**)**



The imine **164** was synthesised from alanine methyl ester hydrochloride (0.708 g, 5.07 mmol) and *para*-chlorobenzaldehyde (0.713 g, 5.07 mmol) in a quantitative yield by the procedure described above. The product was spectroscopically congruent to the data reported by Wang.¹³¹

IR:	824, 1068, 1088, 1204, 1381, 1447, 1589, 1645, 1742 (C=O), 2987.
^1H δ :	1.506 (d, J = 6.6 Hz, 3H), 3.723 (s, 3H), 4.139 (q, J = 6.6 Hz, 1H), 7.358 (d, J = 8.4 Hz, 2H), 7.689 (d, J = 8.4 Hz, 2H), 8.245 (s, 1H).
^{13}C δ :	19.453 (CH ₃), 52.270 (CH ₃), 67.904 (CH), 128.914 (CH), 129.734 (CH), 134.214 (C), 137.129 (C), 161.662 (CH), 172.854 (C=O).

(*E*)-Methyl 2-(4-methoxybenzylideneamino)acetate (165**)**



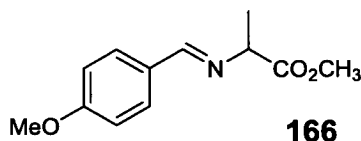
The imine **165** was synthesised from glycine methyl ester hydrochloride (0.928 g, 7.39 mmol) and anisaldehyde (0.898 mL, 7.39 mmol) in a quantitative yield by the procedure described above. The product was spectroscopically congruent to the data reported by Wang.¹³¹

IR: 833, 1029, 1166, 1255, 1578, 1605, 1742 (C=O), 2953.

¹H δ: 3.755 (s, 3H), 3.826 (s, 3H), 4.364 (s, 2H), 6.914 (d, *J* = 8.7 Hz, 2H), 7.705 (d, *J* = 8.7 Hz, 2H), 8.198 (s, 1H).

¹³C δ: 52.202 (CH₃), 55.467 (CH₃), 62.042 (CH), 114.115 (CH), 129.286 (C), 130.250 (CH), 162.034 (C), 164.836 (CH), 171.046 (C=O).

(*E*)-Methyl 2-(4-ethoxybenzylideneamino)propanoate (166)

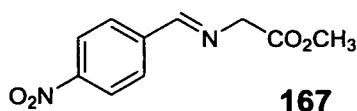


The imine **166** was synthesised from alanine methyl ester hydrochloride (1.00 g, 7.19 mmol) and anisaldehyde (1.00 mL, 7.19 mmol) in a quantitative yield by the procedure described above. The product was spectroscopically congruent to the data reported by Wang.¹³¹

IR: 833, 1029, 1126, 1166, 1253, 1512, 1605, 1740 (C=O), 2936.

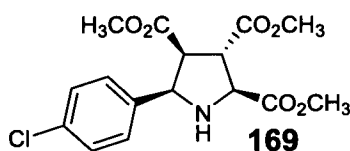
¹H δ: 1.498 (d, *J* = 6.9 Hz, 3H), 3.718 (s, 3H), 3.813 (s, 3H), 4.102 (q, *J* = 6.9 Hz, 1H), 6.901 (d, *J* = 8.7 Hz, 2H), 7.702 (d, *J* = 8.7 Hz, 2H), 8.216 (s, 1H).

¹³C δ: 19.613 (CH₃), 52.217 (CH₃), 55.421 (CH₃), 67.965 (CH), 114.039 (CH), 128.709 (C), 130.204 (CH), 162.072 (C), 162.338 (CH), 172.287 (C=O).

(E)-Methyl 2-(4-nitrobenzylideneamino)acetate (167)

The imine **167** was synthesised from glycine methyl ester hydrochloride (0.597 g, 4.75 mmol) and 4-nitrobenzaldehyde (0.719 g, 4.75 mmol) in a quantitative yield by the procedure described above.

^1H δ : 3.80 (s, 3H), 4.49 (s, 2H), 7.96 (d, $J = 8.9\text{Hz}$, 2H), 8.28 (d, $J = 8.9\text{Hz}$, 2H), 8.39 (s, 1H).

(±)-(2S,3S,4S,5R)-Trimethyl 5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (169)

Method 1:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)acetate (0.209 g, 0.988 mmol) in THF (10 mL) was added lithium bromide (0.129 g, 1.481 mmol), triethylamine (0.165 mL, 1.185 mmol) and dimethyl fumarate (0.142 g, 0.988 mmol). The solution was stirred at room temperature for 72h before saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4). Concentration *in vacuo* followed by removal of excess dimethyl fumarate through sublimation at 45°C at 4 mmHg yielded 0.160 g of pyrrolidine **169**, (46%).

Method 2:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)acetate (0.077 g, 0.364 mmol) in THF (10 mL) was added lithium bromide (0.047 g, 0.546 mmol) and dimethyl fumarate (0.052 g, 0.364 mmol). The solution was heated under reflux for 16h, before being cooled,

followed by addition of saturated ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4). Concentration *in vacuo* followed by removal of excess dimethyl fumarate through sublimation at 45°C at 4 mmHg yielded 0.093 g of pyrrolidine **169**, (72%).

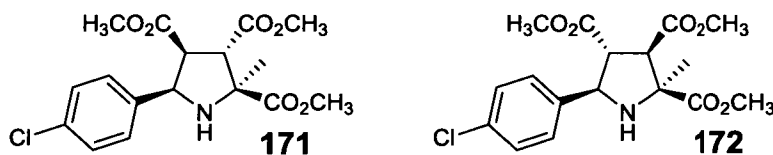
IR: 3342, 2954, 1729, 1491, 1436, 1265, 1215, 1172, 1014, 839, 737.

HRMS (APCI): 356.0900, $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{19}\text{ClNO}_6$: 356.0895.

^1H δ : 2.70 (bs, 1H), 3.216 (s, 3H), 3.530 (dd, $J_1 = 8.1$ Hz, $J_2 = 5.7$ Hz, 1H), 3.626 (dd, $J_1 = 7.5$ Hz, $J_2 = 5.7$ Hz, 1H), 3.731 (s, 3H), 3.796 (s, 3H), 4.162 (d, $J = 7.5$ Hz, 1H), 4.600 (d, $J = 8.1$ Hz, 1H), 7.23-7.25 (m, 4H).

^{13}C δ : 50.402 (CH), 51.746 (CH₃), 52.650 (CH₃), 52.665 (CH₃), 53.500 (CH), 63.128 (CH), 64.548 (CH), 128.375 (CH), 128.435 (CH), 130.949 (C), 136.955 (C), 171.411 (C=O), 172.004 (C=O), 172.520 (C=O).

(±)-(2S,3S,4S,5R)-Trimethyl 5-(4-chlorophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (171)



Method 1:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.226 g, 1.002 mmol) in THF (15 mL) was added lithium bromide (0.131 g, 1.503 mmol), triethylamine (0.168 mL, 1.203 mmol) and dimethyl fumarate (0.130 g, 0.902 mmol). The solution was stirred at room temperature for 72h before saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4). Concentration

in vacuo followed by removal of unreacted dimethyl fumarate through sublimation at 45°C at 4 mmHg yielded 0.205 g of pyrrolidines **171** and **172**, as an inseparable mixture in a 9:1 ratio (62%).

Method 2:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.220 g, 0.974 mmol) in THF (15 mL) was added lithium bromide (0.106 g, 1.218 mmol), triethylamine (0.136 mL, 0.974 mmol) and dimethyl fumarate (0.117 g, 0.812 mmol). The solution was heated under reflux for 16h before saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na₂SO₄). Concentration *in vacuo* followed by purification through silica with a gradient elution 20% - 50% ethyl acetate in hexanes gave 0.265 g of pyrrolidines **171** and **172**, as an inseparable mixture in a 9:1 ratio (88%).

Method 3:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.209 g, 0.924 mmol) in THF (12 mL) was added lithium bromide (0.100 g, 1.155 mmol), and dimethyl fumarate (0.117 g, 0.770 mmol). The solution was stirred at reflux for 16h before saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na₂SO₄). Concentration *in vacuo* followed by purification through silica with a gradient elution 20% - 50% ethyl acetate in hexanes gave 0.225 g of pyrrolidines **171** and **172**, as an inseparable mixture in an 8:3 ratio (79%).

Method 4:

To a solution of 4-chlorobenzaldehyde (0.026 g, 0.186 mmol), lithium bromide (0.024 g, 0.279 mmol) and dimethyl fumarate (0.027 g, 0.186 mmol) in THF (3 mL) was added alanine methyl ester hydrochloride (0.026g, 0.186 mmol) and triethylamine (0.026 mL, 0.186 mmol). The solution was heated under reflux for 16h before saturated ammonium chloride

was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4) and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the crude reaction mixture indicated an approximately 1:1 mixture of pyrrolidines **171** and **172**.

Method 5:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.046 g, 0.204 mmol) in THF (12 mL) was added lithium bromide (0.026 g, 0.306 mmol), dimethyl fumarate (0.029 g, 0.204 mmol) and water (0.004 mL, 0.204 mmol). The solution was heated under reflux for 16h before saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4) and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the crude reaction mixture indicated an approximately 1:1 mixture of pyrrolidines **171** and **172**.

Major Diastereomer (**171**):

IR: 3357, 2953, 1734, 1491, 1437, 1260, 1172, 1015, 832, 700.

MS (EI): 370 (1, $\text{M}+\text{H}^+$), 310 (53), 278 (75), 250 (100), 225 (34), 211 (47), 165 (48).

HRMS (APCI): 370.1058, $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{21}\text{ClNO}_6$: 370.1052.

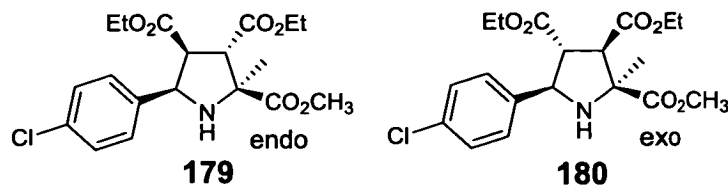
^1H δ : 1.357 (s, 3H), 2.60 (bs, 1H), 3.199 (s, 3H), 3.684 (s, 3H), 3.7- 3.84 (m, 1H), 3.771 (s, 3H), 3.981 (d, 1H, $J = 9.6$ Hz), 4.760 (d, $J = 9.3$ Hz, 1H), 7.23-7.25 (m, 4H).

^{13}C δ : 21.306, 51.393, 52.096, 52.369, 52.984, 53.341, 62.040, 67.016, 128.352, 128.769, 133.568, 138.519, 171.062, 171.206, 174.236.

Minor diastereomer (**172**):

^1H δ : 1.64 (s, 3H), 3.589 (s, 3H), 3.660 (s, 3H), 3.804 (s, 3H), 4.39 (d, $J = 8.7$ Hz, 1H). (Other peaks obscured under the major diastereomer.)

3,4-Diethyl 2-methyl 5-(4-chlorophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (179 + 180)



Method 1:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.109 g, 0.483 mmol) in toluene (5 mL) was added diethyl fumarate (0.079 mL, 0.483 mmol). This solution was heated under reflux for 16h, before being cooled and condensed *in vacuo*. Purification through a bed of silica with a gradient elution, hexanes, 20% then 50% ethyl acetate in hexanes yielded 0.147 g of a 1:2 mixture of **179** and **180** (77%).

Microwave Reactions:

A solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate, diethyl fumarate and lithium bromide in THF (3mL) in a microwave reaction vessel was purged with nitrogen, then sealed and heated in a Biotage microwave reactor using the times and temperatures listed in Table 3. After cooling the reaction saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na₂SO₄).

Concentration *in vacuo* allowed analysis of the crude reaction mixture by ¹H NMR spectroscopy.

IR: 831, 1030, 1093, 1183, 1257, 1376, 1446, 1491, 1732 (C=O), 2923, 3354 (NH).

MS (EI): 398 (3, M+H⁺), 338 (31), 292 (75), 264 (100), 225 (95), 192 (35), 165 (59).

HRMS (APCI): 398.1369, [M+H]⁺ calcd for C₁₉H₂₆ClNO₆: 398.1365.

Major Diastereomer (**180**):

^1H δ : 1.120 (t, J = 7.2Hz, 3H), 1.23 - 1.29 (m, 3H), 1.718 (s, 3H), 3.0 (bs, 1H), 3.40 - 3.52 (m, 1H), 3.723 (s, 3H), 3.72 - 3.93 (m, 1H), , 4.04 - 4.21 (m, 4H), 4.484 (d, J = 9 Hz, 1H), 7.28 - 7.39 (m, 4H).

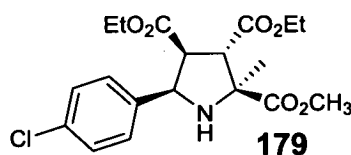
^{13}C δ : 14.18, 14.24, 25.47, 52.80, 55.17, 58.24, 61.45, 64.29, 64.48, 67.63, 128.73, 128.87, 134.04, 138.43, 170.48, 171.72, 173.91.

Minor Diastereomer (**179**):

^1H δ : 0.864 (t, J = 6.9Hz, 3H), 1.404 (s, 3H), 3.850 (s, 3H), 4.806 (d, J = 9Hz, 1H), plus overlapped resonances.

^{13}C δ : 13.77, 14.21, 21.12, 52.15, 53.05, 53.99, 60.95, 61.30, 62.23, 67.18, 128.48, 129.04, 133.78, 138.50, 170.45, 170.83, 174.38.

(\pm)-(2*S*,3*S*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-(4-chlorophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (**179**)

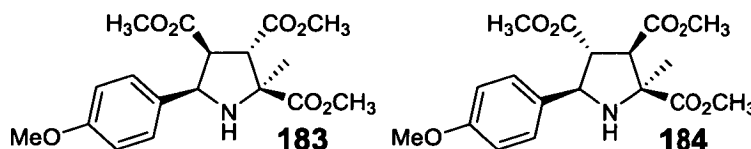


To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.226 g, 1.002 mmol) in THF (15 mL) was added lithium bromide (0.131 g, 1.503 mmol), triethylamine (0.168 mL, 1.203 mmol) and diethyl fumarate (0.092 mL, 0.902 mmol). The solution was stirred at room temperature for 72h before saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4). Concentration *in vacuo* followed by column chromatography with CH_2Cl_2 as eluent followed by 50% ethyl acetate in hexanes gave 117 mg of pyrrolidine **179**, (52%).

^1H δ : 0.84 (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.38 (s, 3H), 3.54 - 3.78 (m, 1H), 3.83 (s, 3H), 4.05 - 4.25 (m, 1H), 4.81 (d, $J = 9.4$ Hz, 1H), 7.22 - 7.30 (m, 4H).

^{13}C δ : 13.73, 14.21, 21.10, 52.09, 53.01, 53.92, 60.89, 61.25, 62.17, 67.09, 128.41, 129.00, 133.68, 138.50, 170.48, 170.82, 174.39.

(\pm)-(2*S*,3*S*,4*S*,5*R*)-Trimethyl 5-(4-methoxyphenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate
/ (\pm)-(2*S*,3*R*,4*R*,5*R*)-trimethyl 5-(4-methoxyphenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (**183** + **184**)



Method 1:

To a solution of (*E*)-methyl 2-(4-methoxybenzylideneamino)propanoate (0.143 g, 0.649 mmol) in THF (12 mL) was added lithium bromide (0.071 g, 0.812 mmol), and dimethyl fumarate (0.078 g, 0.541 mmol). The solution was heated under reflux for 16h before saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4). Concentration *in vacuo* followed by purification through silica with a gradient elution 20% - 50% ethyl acetate in hexanes gave 0.167 g of pyrrolidines **183** and **184**, as an inseparable mixture in a 1.3:1 ratio (84%).

Method 2:

To a solution of (*E*)-methyl 2-(4-methoxybenzylideneamino)propanoate (0.087 g, 0.391 mmol) in THF (5 mL) was added lithium bromide (0.042 g, 0.489 mmol), triethylamine (0.055 mL, 0.391 mmol) and dimethyl fumarate (0.047 mg, 0.326 mmol). The solution was stirred at room temperature for 72h before saturated ammonium chloride was added (10

mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na₂SO₄).

Concentration *in vacuo* followed by column chromatography with a gradient elution of 20% to 50% ethyl acetate in hexanes gave 84 mg of pyrrolidine **183** (71%).

IR: 3326, 2953, 1731, 1612, 1513, 1436, 1249, 1176, 1031, 836.

MS (EI) *m/z*: 366 (4, M+H⁺), 334 (7), 306 (24), 274 (22), 246 (83), 221 (56), 161 (100).

HRMS EI *m/z*: 366.15604, [M+H]⁺ calcd for C₁₈H₂₄NO₇; 366.15473.

Pyrrolidine **183**:

¹H δ: 1.35 (s, 3H), 2.60 bs (1H), 3.18 (s, 3H), 3.54 – 3.62 (m, 1H), 3.68 (s, 3H), 3.74 (s, 3H), 3.82 (s, 3H), 3.95 (d, *J* = 9.5 Hz, 1H), 4.74 (d, *J* = 9.3 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 1H).

¹³C δ: 21.11, 51.60, 52.21, 52.41, 52.92, 53.86, 55.21, 62.43, 67.08, 113.57,

128.43, 131.72, 159.16, 171.15, 171.58, 174.35.

Pyrrolidine **184**:

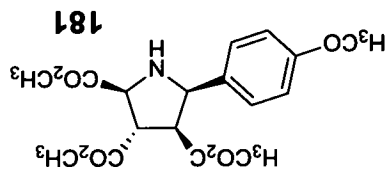
¹H δ: 1.61 (s, 3H), 2.60 (bs, 1H), 3.37 – 3.42 (m, 1H), 3.52 (s, 3H), 3.60 – 3.80 (m,

2H), 3.62 (s, 3H), 3.64 (s, 3H), 3.70 (s, 3H), 4.30 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H).

¹³C δ: 26.10, 52.26, 52.32, 52.48, 52.72, 55.69, 58.67, 65.06, 67.65, 114.10,

128.29, 132.43, 159.49, 171.69, 172.82, 174.53.

(±)-(2*S*,3*S*,4*S*,5*R*)-Trimethyl 5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (**181**)



To a solution of (*E*)-methyl 2-(4-methoxybenzylideneamino)acetate (0.128 g, mmol) in acetonitrile (5 mL) was added silver acetate (0.155 g, mmol), DBU (0.093 mL, mmol) and dimethyl fumarate (0.178 g, mmol). The solution was stirred for 20h before saturated ammonium chloride was added (10 mL) and the mixture extracted with ethyl acetate (3 x 5 mL) and dried (Na₂SO₄). Concentration *in vacuo*, followed by purification on silica with a gradient elution of 20% to 50% ethyl acetate in hexanes gave 103 mg of pyrrolidine **181** (24%).

IR: 3340, 2954, 1734, 1612, 1514, 1436, 1250, 1174, 1032, 914, 838, 732.

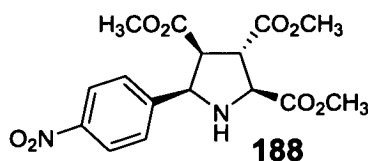
MS (EI) *m/z*: 351 (4), 320 (10), 292 (11), 260 (20), 232 (25), 207 (100), 147 (84).

HRMS EI *m/z*: 351.13112, [M]⁺ calcd for C₁₇H₂₁NO₇ 351.13180.

¹H δ: 2.60 (bs, 1H), 3.243 (s, 3H), 3.63 – 3.74 (m, 2H), 3.768 (s, 3H), 3.836 (s, 3H), 4.230 (d, *J* = 7.5 Hz, 1H), 4.760 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), 8.17 (d, *J* = 9.0 Hz, 2H).

¹³C δ: 50.58, 51.63, 52.52, 52.57, 53.73, 55.16, 63.13, 64.81, 113.57, 127.95, 130.07, 159.15, 171.69, 172.05, 172.55.

(±)-(2*S*,3*S*,4*S*,5*R*)-Trimethyl 5-(4-nitrophenyl)pyrrolidine-2,3,4-tricarboxylate (188**)**



Method 1:

To a solution of (*E*)-methyl 2-(4-nitrobenzylideneamino)acetate (0.036 g, 0.162 mmol) in THF (5 mL) was added lithium bromide (0.021 g, 0.243 mmol) and dimethyl fumarate (0.023 g, 0.162 mmol). The solution was heated under reflux for 16h before saturated ammonium chloride was added (10 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and

dried (Na₂SO₄). Concentration *in vacuo* followed by purification through a plug of silica with 50% ethyl acetate in hexanes as eluent yielded 51 mg of pyrrolidine **188**, (85%).

Method 2:

To a solution of (E)-methyl 2-(4-nitrobenzylideneamino)acetate (0.018 g, 0.081 mmol) in THF (5 mL) was added lithium bromide (0.011 g, 0.122 mmol), triethylamine (0.011 mL, 0.081 mmol) and dimethyl fumarate (0.012 g, 0.081 mmol). The solution was stirred at room temperature for 72h before saturated ammonium chloride was added (8 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na₂SO₄). Concentration *in vacuo* followed by purification through a plug of silica with 50% ethyl acetate in hexanes as eluent yielded 0.020 g of pyrrolidine **188**, (67%).

IR: 3350, 1735, 1521, 1437, 1348, 1217, 1172, 1014, 856.

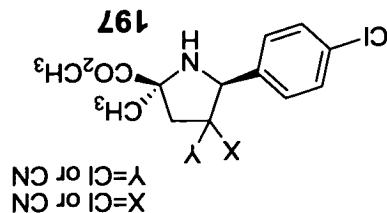
MS (EI) m/z: 366 (4, M⁺), 307 (27), 275 (59), 247 (100), 222 (38), 162 (40).

HRMS EI m/z: 366.10625, [M]⁺ calcd for C₁₆H₁₈N₂O₈: 366.10632.

¹H δ: 2.60 (bs, 1H), 3.243 (s, 3H), 3.63 – 3.74 (m, 2H), 3.768 (s, 3H), 3.836 (s, 3H), 4.230 (d, J = 7.5 Hz, 1H), 4.760 (d, J = 8.1 Hz, 1H), 7.538 (d, J = 9.0 Hz, 2H), 8.167 (d, J = 9.0 Hz, 2H).

¹³C δ: 50.26, 52.12, 52.59, 53.01, 53.37, 63.11, 64.38, 123.65, 128.22, 146.28, 147.71, 171.15, 172.06, 172.50.

(±)-(2S,5S)-Methyl 4-chloro-5-(4-chlorophenyl)-4-cyano-2-methylpyrrolidine-2-carboxylate (**197**)



Method 1:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.152 g, 0.674 mmol) in THF (8 mL) was added lithium bromide (0.088 g, 1.010 mmol) and 2-chloroacrylonitrile (0.054 mL, 0.674 mmol). The mixture was heated under reflux for 20h, then cooled and saturated ammonium chloride was added (10 mL). The mixture was then extracted with ethyl acetate (3 x 5 mL), then dried (Na₂SO₄). Concentration *in vacuo*, followed by purification through a bed of silica gel with 50% ethyl acetate / hexanes yielded 106 mg of inseparable diastereomers **197**, (50%).

Method 2:

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.178 g, 0.788 mmol) in THF (8 mL) was added lithium bromide (0.103 g, 1.183 mmol), 2-chloroacrylonitrile (0.063 mL, 0.788 mmol) and triethylamine (0.110 mL, 0.788 mmol). The mixture was stirred at room temperature for 24h, before saturated ammonium chloride was added (10 mL). The mixture was then extracted with ethyl acetate (3 x 5 mL), then dried (Na₂SO₄) and concentrated *in vacuo*. Analysis of the crude reaction mixture by ¹H NMR indicated a 7:4 ratio of diastereomers **197**, in less than 20% yield.

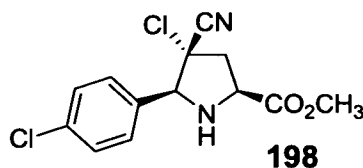
IR: 3344, 2963, 2220, 2190, 1729, 1594, 1487, 1261, 1093, 1015, 800.

MS (EI) *m/z*: 313 (1, M+H⁺), 274 (34), 243 (27), 217 (35), 165 (32), 139 (100), 111 (33).

HRMS APCI *m/z*: 313.0512, [M+H]⁺ calcd for C₁₄H₁₄Cl₂N₂O₂: 313.0505.

¹H δ: 1.54 (s, 1.5H), 1.56 (s, 1.5H), 2.46 (d, *J* = 13.5 Hz, 0.5H), 2.68 (d, *J* = 13.5 Hz, 0.5H), 3.27 (d, *J* = 13.5 Hz, 0.5H), 3.51 (d, *J* = 13.5 Hz, 0.5H), 3.81 (s, 1.5H), 3.838 (s, 1.5H), 4.48 (s, 0.5H), 4.69 (s, 0.5H), 7.38 – 7.52 (m, 4H).

¹³C δ: 26.26, 27.33, 34.59, 34.75, 52.08, 53.20, 53.33, 53.37, 63.04, 65.65, 66.40, 72.18, 111.04, 116.65, 128.25, 128.86, 128.97, 129.23, 131.23, 131.52, 136.97, 138.70, 173.33, 173.36.

(±)-(2S,4R,5S)-Methyl 4-chloro-5-(4-chlorophenyl)-4-cyanopyrrolidine-2-carboxylate (198)

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)acetate (0.290 g, 1.370 mmol) in THF (8 mL) was added lithium bromide (0.178 g, 2.050 mmol) and 2-chloroacrylonitrile (0.109 mL, 1.365 mmol). The mixture was heated in a Biotage microwave reactor for 15 min at 150°C then cooled and saturated ammonium chloride was added (10 mL). The mixture was then extracted with ethyl acetate (3 x 5 mL), then dried (Na₂SO₄). Concentration *in vacuo*, followed by purification *via* column chromatography with a 0 - 50% ethyl acetate in hexanes gradient elution yielded 102 mg of **198**, (25%).

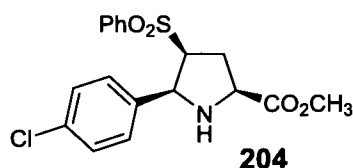
IR: 3355, 2956, 2227, 1729, 1492, 1437, 1217, 1093, 1015, 832, 736.

MS (EI) *m/z*: 298(3%, M⁺), 239 (34), 211(38), 179(18), 168 (16), 151 (100), 140(17), 89 (18).

HRMS-EI *m/z*: 298.02772 [M]⁺ calcd for C₁₃H₁₂N₂O₂Cl₂: 298.02758.

¹H δ (500MHz): 2.790 (dd, *J*₁ = 14.1 Hz, *J*₂ = 8.6 Hz, 1H), 2.864 (bs, 1H), 3.050 (dd, *J*₁ = 14.1 Hz, *J*₂ = 6.5 Hz, 1H), 3.838 (s, 3H), 4.204 (m, 1H), 4.527 (d, *J* = 5.5 Hz, 1H), 7.395 (d, *J* = 8.5 Hz, 2H), 7.521 (d, *J* = 8.5 Hz, 2H).

¹³C δ (125MHz): 44.31 (CH), 52.84 (CH), 56.88 (CH₃), 60.73 (CH), 73.62 (C), 116.52 (CN), 128.91 (CH) (2 overlapped), 133.87 (C), 135.39 (C), 172.00 (C=O).

(±)-(2S,4S,5S)-Methyl 5-(4-chlorophenyl)-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (204)

To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)acetate (0.101 g, 0.476 mmol) in THF (5 mL) was added lithium bromide (0.015 g, 0.178 mmol), triethylamine (0.025 mL, 0.178 mmol) and phenyl vinyl sulfone (0.020 g, 0.119 mmol). The solution was stirred at room temperature for 72h before saturated ammonium chloride was added (8 mL) and the mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na₂SO₄). Concentration *in vacuo* followed by purification by flash chromatography with 20% ethyl acetate in hexanes, followed by neat ethyl acetate as eluent yielded 0.019 g of pyrrolidine **204**, (42%).

IR 3343, 2953, 1743, 1491, 1306, 1208, 1147, 1087, 1014, 827.

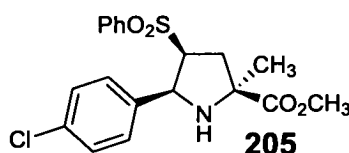
MS (EI) *m/z*: 380 (1, M+H⁺), 361 (2), 237 (33), 211 (21), 178 (100), 143 (20).

HRMS (APCI) *m/z*: 380.0724, [M+H]⁺ calcd for C₁₈H₁₈ClNO₄S: 380.0718.

¹H δ: 2.25 – 2.38 (m, 1H), 2.58 – 2.70 (m, 1H), 3.52 – 3.63 (m, 1H), 3.76 (s, 3H), 4.08 – 4.20 (m, 1H), 4.74 (d, *J* = 5.8 Hz, 1H), 7.18 – 7.20 (m, 4H), 7.47 – 7.84 (m, 5H).

¹³C δ: 31.00, 52.51, 59.30, 61.92, 70.28, 128.39, 128.61, 128.79, 129.50, 133.68, 134.13, 137.96, 139.91, 173.31.

(±)-(2*S*,4*S*,5*S*)-Methyl 5-(4-chlorophenyl)-2-methyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (205)



To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.142 g, 0.628 mmol) in THF (10 mL) was added lithium bromide (0.082 g, 0.9442 mmol) and phenyl vinyl sulfone (0.048 g, 0.285 mmol). The solution was heated under reflux for 20h, before being cooled,

followed by addition of saturated ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4). Concentration *in vacuo* led to a residue which was purified by flash chromatography with a gradient elution of 20% ethyl acetate in hexanes followed by neat ethyl acetate to yield 0.060 g of pyrrolidine **205**, (53%).

IR: 3350, 2951, 1737, 1491, 1447, 1306, 1148, 1089, 1014 829.

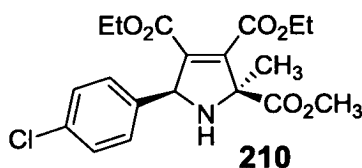
MS (EI) m/z : 394 (3, $\text{M}+\text{H}^+$), 334 (25), 225 (10), 192 (100), 165 (26), 115 (25), 71 (27).

HRMS (APCI) m/z : 394.0876, $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{ClNO}_4\text{S}$: 394.0874.

^1H δ : 1.54 (s, 3H), 2.33 – 2.52 (m, 1H), 2.67 – 2.78 (m, 1H), 3.69 (s, 3H), 3.72 – 3.87 (m, 1H), 4.67 (d, $J = 8.3$ Hz, 1H), 7.10 – 7.17 (m, 4H), 7.36 – 7.73 (m, 5H).

^{13}C δ : 26.07, 38.87, 52.97, 62.59, 65.25, 70.26, 128.45, 128.79, 128.85, 129.40, 131.20, 133.79, 134.03, 138.87, 176.24.

(2S,5S)-3,4-Diethyl 2-methyl 5-(4-chlorophenyl)-2-methyl-2,5-dihydro-1H-pyrrole-2,3,4-tricarboxylate (210)



To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.118 g, 0.523 mmol) in THF (20 mL) was added lithium bromide (0.068 g, 0.784 mmol), triethylamine (0.087 mL, 0.627 mmol) and diethyl acetylene dicarboxylate (0.092 mL, 0.575 mmol). The solution was stirred at room temperature for 72h before saturated ammonium chloride was added (8 mL) and the mixture was extracted with ethyl acetate (3 x 10 mL) and dried (Na_2SO_4). Concentration *in vacuo* followed by purification *via* flash chromatography with

dichloromethane followed by 50% ethyl acetate / hexanes as eluent yielded 0.043 g of pyrroline **210**, (21%).

IR: 3364, 2983, 1728, 1573, 1447, 1370, 1255, 1158, 1129, 1050, 789.

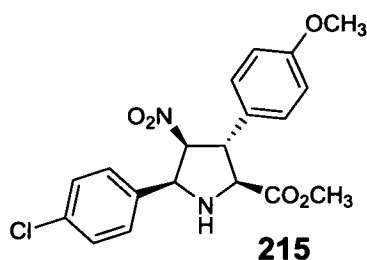
MS (EI) m/z : 396 (6, $M+H^+$), 336 (94), 322 (20), 290 (34), 264 (93), 234 (77), 218 (100), 192 (75), 100 (40).

HRMS APCI m/z : 396.1214, $[M+H]^+$ calcd for $C_{19}H_{23}ClNO_6$ 396.1208.

1H δ : 1.22 (t, $J = 7.1$ Hz, 3H), 1.37 (t, $J = 7.1$ Hz, 3H), 1.68 (s, 3H), 3.80 (s, 3H), 4.28 (q, $J = 7.1$ Hz, 2H), 4.39 (q, $J = 7.1$ Hz, 2H), 4.59 (s, 1H), 7.30 - 7.31 (m, 4H).

^{13}C δ : 13.91, 14.14, 24.75, 53.07, 59.21, 61.45, 61.71, 68.48, 128.92, 129.38, 134.21, 138.91, 141.18, 153.94, 162.97, 165.82, 167.93.

(\pm)-(2*S*,3*R*,4*S*,5*S*)-Methyl 5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine-2-carboxylate (215**)**



To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)acetate (0.509 g, 2.405 mmol) in THF (15 mL) was added lithium bromide (0.209 g, 2.405 mmol) and (*E*)-1-methoxy-4-(2-nitrovinyl)benzene (0.431 g, 2.405 mmol). The solution was heated under reflux for 24h, before being cooled, followed by addition of saturated ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4). Concentration *in vacuo* led to a residue which was purified by flash chromatography with a gradient elution of 15% ethyl acetate in hexanes followed by neat ethyl acetate to yield 0.600 g of pyrrolidine **215**, (64%).

IR: 3335, 2955, 1739, 1612, 1550, 1515, 1436, 1252, 1182, 1032, 1015, 829.

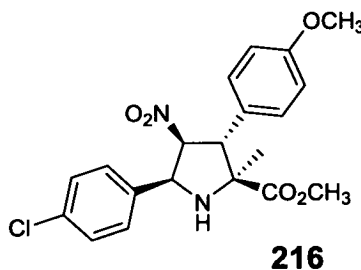
MS (EI) m/z : 391 (1, $M+H^+$), 343 (3), 284 (30), 257 (100), 222 (10), 179 (10), 151 (35).

HRMS APCI m/z : 391.1059, $[M+H]^+$ calcd for $C_{19}H_{19}ClN_2O_5$: 391.1055.

1H δ : 3.20 (bs, 1H), 3.79 (d, $J = 1.5$ Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 4.91 (d, $J = 6.6$ Hz, 1H), 5.22 (dd, $J_1 = 6.6$ Hz, $J_2 = 3.6$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 2H), 7.22 (d, $J = 8.7$ Hz, 2H), 7.28 – 7.36 (m, 4H).

^{13}C δ : 52.98, 54.36, 55.49, 66.62, 67.09, 96.75, 114.84, 128.07, 128.73, 129.16, 130.03, 132.90, 134.93, 159.55, 171.63.

(\pm)-(2*S*,3*S*,4*S*,5*S*)-Methyl 5-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-methyl-4-nitropyrrolidine-2-carboxylate (216**)**



To a solution of (*E*)-methyl 2-(4-chlorobenzylideneamino)propanoate (0.625 g, 2.77 mmol) in THF (20 mL) was added lithium bromide (0.241 g, 0.546 mmol) and (*E*)-1-methoxy-4-(2-nitrovinyl)benzene (0.546 g, 3.05 mmol). The solution was heated under reflux for 24h, before being cooled, followed by addition of saturated ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (3 x 5 mL) and dried (Na_2SO_4). Concentration *in vacuo* led to a residue which was purified by flash chromatography with a gradient elution of 10% ethyl acetate in hexanes followed by neat ethyl acetate to yield 1.10 g of pyrrolidine **216**, (>95%).

IR: 3350, 2954, 1735, 1612, 1551, 1516, 1253, 1182, 1093, 853.

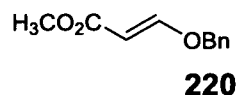
MS (EI) m/z : 345 (6), 298 (19), 257 (100), 219 (11), 165 (10).

HRMS APCI m/z : 405.1217, $[M+H]^+$ calcd for $C_{20}H_{21}ClN_2O_5$: 405.1212.

1H δ : 1.20 (s, 3H), 3.21 (s, 3H), 3.86 (s, 3H), 4.48 (d, $J = 6.9$ Hz, 1H), 5.06 (d, $J = 7.8$ Hz, 1H), 5.59 (dd, $J_1 = 7.8$ Hz, $J_2 = 6.9$ Hz, 1H), 6.89 (d, 8.7 Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H), 7.31 – 7.38 (m, 4H). (N-H Not observed).

^{13}C δ : 21.19, 53.12, 55.41, 55.74, 63.77, 68.66, 95.25, 114.29, 127.04, 128.49, 128.98, 129.76, 131.47, 134.84, 159.48, 174.67.

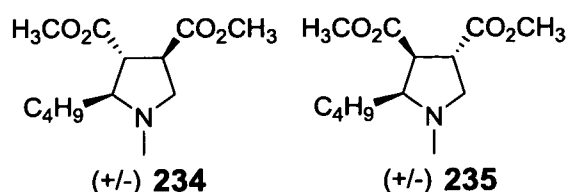
(*E*)-Methyl 3-(benzyloxy)acrylate (220**)**



To a solution of methyl propiolate (2.08 mL, 24.89 mmol) in CH_2Cl_2 (35 mL) was added benzyl alcohol (2.58 mL, 24.89 mmol) and triethylamine (0.350 mL, 2.489 mmol). The reaction was stirred for 16h, before water (50 mL) was added. The organic layer was separated, washed with water (30 mL) and dried ($MgSO_4$). The organic layer was concentrated *in vacuo*, then distilled with Kugelrohr apparatus at 110°C (0.4 mmHg) to yield 2.73 g of **220** as a clear oil, (57%).

1H δ : 3.70 (s, 3H), 4.90 (s, 2H), 5.32 (d, $J = 12.6$ Hz, 1H), 7.30 – 7.46 (m, 5H), 7.68 (d, $J = 12.6$ Hz, 1H).

(\pm)-(2*S*,3*R*,4*R*)-Dimethyl 2-butyl-1-methylpyrrolidine-3,4-dicarboxylate/ (\pm)-(2*S*,3*S*,4*S*)-dimethyl 2-butyl-1-methylpyrrolidine-3,4-dicarboxylate (234** + **235**)**



To a solution of sarcosine (0.140 g, 1.57 mmol), and valeraldehyde (0.167 mL, 1.57 mmol) in toluene (8 mL) was added dimethyl fumarate (0.226 g, 1.57 mmol). The mixture was heated under reflux under Dean-Stark conditions for 3h, before being cooled. To the cooled solution was added 10 mL of saturated ammonium chloride solution and the organic layer separated. Extraction of the aqueous layer with (2 x 5 mL) ethyl acetate followed by combining of the organic layers, washing with water (1 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification through a bed of silica gel with 50% ethyl acetate / hexanes as eluent gave 264 mg of a 3:2 ratio of an inseparable mixture of diastereomers **234** and **235** (65%).

IR: 3453, 2956, 1729, 1594, 1437, 1199, 1172, 1030.

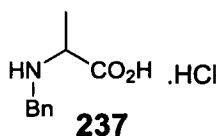
MS (EI) m/z : 257 (M^+ , 5), 226 (21), 200 (43), 168 (100), 140 (99), 108 (17), 82 (24).

HRMS-EI m/z : 257.16280, $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_4$ 257.16271.

^1H δ : 0.80 - 0.86 (m, 3H), 1.18 - 1.62 (m, 12H), 2.23 (s, 1.66H), 2.27 (s, 1.33H), 2.29 - 2.38 (m, 1H), 2.44 - 2.58 (m, 1H), 3.12 - 3.22 (m, 1H), 3.29 - 3.42 (m, 2H), 3.64 (s, 1.5H), 3.66 (s, 1.5H), 3.66 (s, 3H).

^{13}C δ : 14.15, 14.19, 22.66, 23.16, 27.10, 28.75, 29.61, 31.58, 40.20, 40.91, 44.70, 45.20, 49.75, 50.96, 52.08, 52.35, 52.51, 52.57, 58.85, 58.91, 68.89, 69.95, 173.35, 173.82, 173.95, 174.73.

2-(Benzylamino)propanoic acid hydrochloride (*N*-benzyl alanine hydrochloride) (**237**)



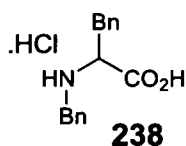
The procedure outlined above for the synthesis of **214** was followed for the synthesis of **215** from DL-alanine (5.555 g, 62.4 mmol), sodium hydroxide (2.62 g, 65.5 mmol),

benzaldehyde (8.89 mL, 87.0 mmol) and sodium borohydride (3.07 g, 81.0 mmol) to give 9.01 g of **215** (67%).

^1H δ (D_2O): 0.92 (d, $J = 7.0\text{ Hz}$, 3H), 2.95 (q, $J = 7.0\text{ Hz}$, 1H), 3.37 (d, $J = 12.5\text{ Hz}$, 1H), 3.53 (d, $J = 12.5\text{ Hz}$, 1H), 7.08 – 7.29 (m, 5H), exchangeable H's not observed.

^{13}C δ (D_2O): 18.43, 51.20, 58.28, 127.46, 128.77, 128.80, 139.07, 183.57.

(\pm)-2-(Benzylamino)-3-phenylpropanoic acid hydrochloride (238**)**

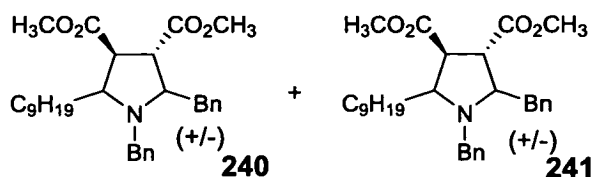


To a solution of DL-phenylalanine (0.240 g, 1.453 mmol) in methanol (10 mL), was added sodium hydroxide (0.061 g, 1.526 mmol) and the reaction allowed to stir for 5 minutes before benzaldehyde (0.207 mL, 2.034 mmol) was added and the reaction stirred for 15 min. After this time the reaction was cooled to 0°C and sodium borohydride (0.071 g, 1.889 mmol) was added. The reaction was stirred for 30 min, then the methanol was removed *in vacuo*. Water was added (5 mL) followed by 2M HCl (2 mL). The resulting solid was collected by filtration and washed with ice cold water (2 mL) and ice cold methanol (1 mL). The solid was dried under vacuum, yielding 314 mg of **238** (74%).

^1H δ (D_2O): 2.54 – 2.71 (m, 2H), 3.08 (dd, $J_1 = 7.6\text{ Hz}$, $J_2 = 6.1\text{ Hz}$, 1H), 3.30 (d, $J = 12.6\text{ Hz}$, 1H), 3.48 (d, $J = 12.6\text{ Hz}$, 1H), 6.89 – 7.23 (m, 10H), exchangeable not observed.

^{13}C δ (D_2O): 31.06, 51.04, 64.47, 126.66, 127.42, 128.58, 128.70 (overlapped), 129.31, 137.99, 138.81, 181.25.

(±)-Dimethyl 1,2-dibenzyl-5-nonylpyrrolidine-3,4-dicarboxylate / (±)-dimethyl 1,2-dibenzyl-5-nonylpyrrolidine-3,4-dicarboxylate (240 + 241)



To a solution of *N*-benzylphenylalanine (sodium chloride mixture) (0.052 g, 0.165 mmol), and decanal (0.026 mg, 0.165 mmol) in toluene (3 mL) was added dimethyl fumarate (0.024 g, 0.165 mmol). The mixture was heated under reflux under Dean-Stark conditions for 16h, before being cooled. To the cooled solution was added 5 mL of saturated ammonium chloride solution and the organic layer separated. Extraction of the aqueous layer with (2 x 5 mL) ethyl acetate followed by washing the combined extracts with water (1 x 5 mL), dried Na_2SO_4 and concentration *in vacuo* gave the crude product. Chromatography on silica gel with 20% ethyl acetate in hexanes, followed by 50% ethyl acetate / hexanes as eluent gave an inseparable 1:1 mixture of diastereomers **240** and **241**, 27 mg (33%).

IR: 2926, 2855, 1730, 1436, 1207, 1173, 700.

MS (EI) *m/z*: 457 (4), 425 (6), 402 (10), 339 (10), 280 (11), 230 (8), 155 (10), 91 (100).

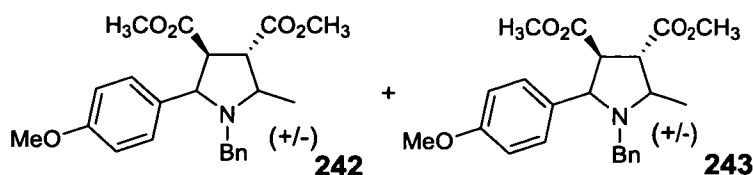
HRMS APCI *m/z*: 494.3260, $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{43}\text{NO}_4$ 494.3265.

^1H δ : 0.87 (t, $J = 6.4$ Hz, 6H), 1.16 – 1.48 (m, 32H), 2.30 – 2.64 (m, 6H), 2.89 (dd, $J_1 = 14.1$ Hz, $J_2 = 6.0$ Hz, 1H), 2.99 (dd, $J_1 = 14.1$ Hz, $J_2 = 6.0$ Hz, 0.8H (1H)), 3.08 – 3.14 (m, 2H), 3.21 – 3.26 (m, 2H), 3.29 (s, 2.4H (3H)), 3.50 (s, 3H), 3.54 – 3.67 (m, 4H), 3.69 (s, 2.4H (3H)), 3.72 (s, 3H), 6.90–7.04 (m, 4H), 7.11–7.32 (m, 16H).

^{13}C δ : 14.35 (overlapped 2xC), 22.91 (overlapped), 25.10, 26.54, 28.94, 29.39, 29.53, 29.59, 29.62, 29.67, 29.78, 29.97, 30.03, 30.41, 32.12 (overlapped), 33.46, 34.78, 48.69, 48.93, 49.88, 50.59, 51.67, 51.76, 51.99, 52.24, 52.39,

62.04, 63.01, 63.99, 65.27, 126.12, 126.20, 126.96, 127.04, 128.26, 128.38, 128.41, 128.44, 128.55, 128.69, 129.29, 129.62, 138.98, 139.10, 139.45, 139.55, 172.90, 174.13, 174.46, 175.05.

(±)-Dimethyl 1-benzyl-2-(4-methoxyphenyl)-5-methylpyrrolidine-3,4-dicarboxylate / (±)-dimethyl 1-benzyl-2-(4-methoxyphenyl)-5-methylpyrrolidine-3,4-dicarboxylate (242** + **243**)**



To a solution of *N*-benzylalanine (sodium chloride mixture) (0.994 g, 4.18 mmol), and anisaldehyde (0.254 mL, 2.092 mmol) in toluene (5 mL) was added dimethyl fumarate (0.201 g, 1.395 mmol). The mixture was heated under reflux under Dean-Stark conditions for 16h, before being cooled and saturated ammonium chloride added (10 mL). The mixture was extracted with ethyl acetate (2 x 5 mL) then the combined organic extracts were washed with water (1 x 5 mL), dried (Na₂SO₄), concentrated, then purified by chromatography on silica gel with a gradient elution of 20% - 100% ethyl acetate in hexanes, to give an inseparable mixture of an approximately 1:1 mix of diastereomers **242** and **243**, 540 mg (97%).

IR: 2951, 2837, 1738, 1733, 1684, 1601, 1511, 1436, 1249, 1172, 1030, 833, 700.

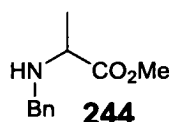
MS (EI)*m/z*: 276 (2), 246 (4), 226 (76), 136 (62), 121 (100), 106 (32), 91 (74).

¹H NMR δ: 0.90 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H), 3.05 (dd, *J*₁ = 5.8 Hz, *J*₂ = 2.9 Hz, 1H), 3.09 – 3.14 (m, 1H), 3.14 (s, 3H), 3.26 – 3.44 (m, 2H), 3.51 – 3.70 (m, 6H), 3.64 (s, 6H, overlap), 3.72 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 4.07 (d, *J* =

7.0 Hz, 1H), 4.11 (d, $J = 7.0$ Hz, 1H), 6.82 – 6.90 (m, 4H), 7.20 – 7.35 (m, 12H), 7.40 (d, $J = 8.5$ Hz, 2H).

^{13}C NMR δ : 8.87, 13.89, 49.07, 49.28, 49.95, 51.28, 51.42, 51.85, 52.11, 52.25, 52.52, 54.14, 54.78, 55.21, 55.59, 57.34, 65.73, 67.51, 113.93, 114.33, 126.70, 126.93, 127.96, 128.21, 128.27, 128.37, 129.24, 129.72, 131.56, 133.30, 138.89, 139.18, 159.14, 159.22, 172.18, 172.28, 173.92, 174.06.

(±)-Methyl 2-(benzylamino)propanoate (244)

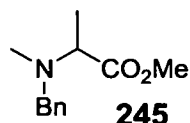


A solution of alanine methyl ester hydrochloride (6.554 g, 47.0 mmol) was dissolved in methanol and triethylamine (6.54 mL, 47.0 mmol) was added and stirred for 10 min. Benzaldehyde (4.78 mL, 47.0 mmol) was added and the reaction stirred for 40 min. The mixture was then cooled to 0°C and sodium borohydride (3.55 g, 94.0 mmol) was added. The mixture was stirred for 30 min, before the methanol was removed *in vacuo*. To the residue was added water (50 mL) and ethyl acetate (20 mL). The organic layer was separated, and the aqueous was extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo* to yield **244** 9.0 g (>95%).

IR: 3326, 2980, 1736, 1453, 1200, 1153, 1066, 737, 699.

^1H δ : 1.35 (d, $J = 7.0$ Hz, 3H), 3.42 (q, $J = 7.0$ Hz, 1H), 3.70 (d, $J = 12.9$ Hz, 1H), 3.73 (s, 3H), 3.82 (d, $J = 12.9$ Hz, 1H), 7.23 - 7.38 (m, 5H).

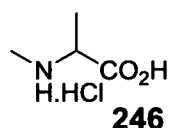
^{13}C δ : 18.98, 51.89, 52.06, 55.84, 127.41, 128.55, 128.61, 139.09, 175.86.

(±)-Methyl 2-(benzyl(methyl)amino)propanoate (245)

A solution of *N*-benzylalanine methyl ester **244** (1.08 g, 5.59 mmol) was dissolved in methanol (10 mL), and paraformaldehyde was added (0.252 g, 8.38 mmol). To this solution was added sodium cyanoborohydride (0.421 g, 6.71 mmol) and the reaction was stirred for 16h. The reaction was quenched by the addition of water (2 mL), and concentrated *in vacuo*. The residue was dissolved in water (15 mL) and ethyl acetate (15 mL), and the organic layer separated, washed with water (2 x 10 mL) and dried (MgSO₄). Concentration *in vacuo*, followed by chromatography with 30% ethyl acetate in hexanes gave 872 mg of **245** (75%).

¹H δ: 1.34 (d, *J* = 7.1 Hz, 3H), 2.29 (s, 3H), 3.49 (q, *J* = 7.1 Hz, 1H), 3.62 (d, *J* = 13.5Hz, 1H), 3.73 (s, 3H), 3.73 (d, *J* = 13.5Hz, 1H), 7.18 – 7.40 (m, 5H).

¹³C δ: 14.93, 38.01, 51.41, 58.42, 60.72, 121.17, 128.39, 128.94, 139.21, 173.86.

(±)-*N*-Methylalanine hydrochloride (2-(methylamino)propanoic acid hydrochloride) (246)**Method 1:**

A solution of **245** (0.709 g, 3.42 mmol) was dissolved in methanol and hydrogenated under 1 atm of H₂ with palladium hydroxide on carbon (20% w/w) (24 mg) for 16h. The reaction was filtered through a plug of Celite™ then concentrated *in vacuo*. Filtration through a bed of silica with 1:1 (ethyl acetate / hexanes), which was then evaporated and 6M HCl (10 mL)

added and the solution refluxed for 16h. The solution was then concentrated under reduced pressure to yield 460 mg of **246** (>95%).

Method 2:

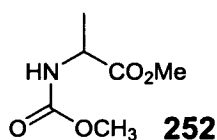
A solution of **254** (11.56 g, 66.0 mmol) was heated under reflux in 6M HCl (50 mL) for 16h.

The solution was then concentrated *in vacuo* to yield 9.01g of **246** (>95% yield).

^1H δ (D_2O): 1.59 (d, $J = 7.2\text{Hz}$, 3H), 2.82 (s, 3H), 3.77 (q, $J = 7.2\text{ Hz}$, 1H), exchangeable not observed.

^{13}C δ (D_2O): 14.88, 31.39, 58.97, 175.11.

(\pm)-Methyl 2-(methoxycarbonylamino)propanoate (252)

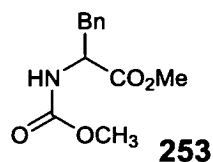


To a solution of (\pm)-alanine methyl ester hydrochloride (3.12 g, 22.34 mmol) in water (10 mL) and toluene (10 mL) was added potassium carbonate (9.26 g, 67.0 mmol). After stirring for 10 min, methyl chloroformate (2.57 mL, 33.5 mmol) was added slowly over 10 min. The reaction was stirred for 6 h, before water was added (20 mL) and the mixture extracted with ethyl acetate (3 x 10 mL) and dried (MgSO_4). Concentration *in vacuo* yielded 3.21 g of **252** (89%).

^1H δ : 1.32 (d, $J = 7.2\text{Hz}$, 3H), 3.60 (s, 3H), 3.67 (s, 3H), 4.22-4.35 (m, 1H), 5.48 (bs, 1H).

^{13}C δ : 18.41, 49.50, 52.17, 52.35, 156.35, 173.62.

IR: 3340, 2956, 1725, 1534, 1455, 1257, 1217, 1079, 782.

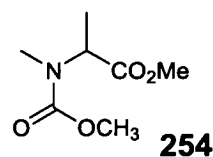
(±)-Methyl 2-(methoxycarbonylamino)-3-phenylpropanoate (253)

Compound **253** was prepared using the method described above for the synthesis of **252** from (±)-phenylalanine methyl ester hydrochloride (14.000 g, 64.9 mmol), potassium carbonate (26.9 g, 195 mmol) and methyl chloroformate (7.4 mL, 97 mmol) to yield 15.20 g of the title compound (>95% yield).

IR: 3045, 1726, 1527, 1458, 1354, 1216, 1060, 701.

^1H δ : 3.04 – 3.13 (m, 2H), 3.63 + 3.64 (s, 3H, rotamers), 3.69 + 3.70 (s, 3H, rotamers), 4.57-4.66 (m, 1H), 5.26 (bs, 1H), 7.08 – 7.34 (m, 5H).

^{13}C δ : 38.30, 52.40, 54.88, (missing 58 predicted), 127.22, 128.69, 129.32, 135.88, 156.41, 172.22

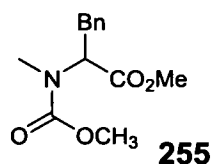
(±)-Methyl 2-(methoxycarbonyl(methyl)amino)propanoate (254)

To a solution of **252** (17.21 g, 107 mmol) in DMF (20 mL) and THF (40 mL) was added sodium hydride (3.08 g, 128 mmol) (60% dispersion in mineral oil) followed by iodomethane (8.01 mL, 128 mmol). The mixture was stirred for 16 h before water was added (100 mL) and the mixture extracted with 1:1 ethyl acetate / hexanes (4 x 20 mL) and dried (MgSO_4). Concentration *in vacuo* gave 11.56 g of **254** (62% yield), shown by NMR to be present as a 2:1 mix of rotamers.

IR: 2956, 1739, 1703, 1455, 1394, 1318, 1220, 1159, 1098, 774.

^1H δ :	1.38 (d, $J = 7.5\text{Hz}$, 3H), 2.35 (s, 1.8H), 2.38 (s, 1.2H), 3.69 (s, 3H), 4.64 (q, $J = 7.5\text{Hz}$, 0.33H), 4.86 (q, $J = 7.5\text{Hz}$, 0.66H).
^{13}C δ :	(14.83, 15.32), (29.79, 30.20), (52.30, 52.98), 54.15, (60.47, 60.58), (157.26, 157.55), (172.52, 172.64).

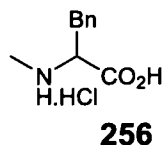
(\pm)-Methyl 2-(methoxycarbonyl(methyl)amino)-3-phenylpropanoate (255)



Compound **255** was prepared as per the method outlined for the synthesis of **254** from **253** (10.62 g, 44.8 mmol), sodium hydride (60%) (1.289 g, 53.7 mmol) and iodomethane (3.36 mL, 53.7 mmol) to yield 9.10 g (81%).

^1H δ :	2.75 + 2.81 (s, 3H, rotamers), 2.90- 3.07 (m, 1H), 3.21 – 3.40 (m, 1H), 3.56 + 3.64 (s, 3H, rotamers), 3.72 (s, 3H), 4.76 (dd, $J_1 = 10.5\text{ Hz}$, $J_2 = 5.2\text{ Hz}$, 0.45H), 4.99 (dd, $J_1 = 10.5\text{ Hz}$, $J_2 = 5.2\text{ Hz}$, 0.55 H), 7.11 – 7.32 (m, 5H).
^{13}C δ :	(31.51, 32.00), (34.97, 35.45), 52.36, (52.88, 52.94), (60.12, 60.59), 126.74, 128.59, 128.87, 137.19, (171.36, 171.64), 1 resonance not observed or overlapped.
IR:	2955, 1743, 1700, 1456, 1393, 1316, 1220, 1140, 1010.

(\pm)-*N*-Methylphenylalanine hydrochloride (2-(methylamino)-3-phenylpropanoic acid hydrochloride) (256)

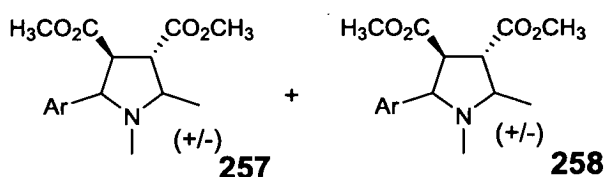


Compound **256** was prepared from **255** (0.519 g, 2.065 mmol) as per method 2 reported previously for the synthesis of **246**, yielding 440 mg (>95%).

^1H δ (D_2O): 2.68 (s, 3H), 3.23 (d, J = 6.1 Hz, 2H), 3.89 (t, J = 6.1 Hz, 1H), 6.89 – 7.61 (m, 5H), exchangeable H's not observed.

^{13}C δ (D_2O): 34.73, 38.28, 67.06, 130.50, 131.79, 132.08, 137.12, 175.26.

(\pm)-Dimethyl 2-(4-methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-dicarboxylate / (\pm)-dimethyl 2-(4-methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-dicarboxylate (**257** + **258**)



To a solution of *N*-methylalanine (sodium chloride complex) (0.195 g, 1.207 mmol), and anisaldehyde (0.092 mL, 0.756 mmol) in toluene (5 mL) was added dimethyl fumarate (0.0545 g, 0.378 mmol). The mixture was heated under reflux under Dean-Stark conditions for 16h, before being cooled. To the cooled solution was added 10 mL of saturated ammonium chloride solution and the organic layer separated. Extraction of the aqueous layer with (2 x 5 mL) ethyl acetate followed by combining of the organic layers, washing with water (1 x 5mL), dried Na_2SO_4 and concentration *in vacuo*. Chromatography of the residue on silica gel with dichloromethane (50 mL) followed by ethyl acetate (50 mL) as eluent led to 114 mg (94%) of a 1:1 mixture of inseparable diastereomers **257** and **258** a light yellow oil.

IR: 2952, 1734, 1610, 1512, 1437, 1249, 1172, 1031, 843.

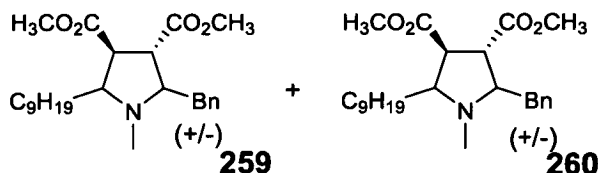
MS (EI) m/z : 321 (16%, M^+), 306 (56), 274 (36), 246 (39), 221 (26), 176 (100), 162 (23).

HRMS-El m/z : 321.15723 $[M]^+$ calcd for $C_{17}H_{23}NO_5$: 321.15762

1H δ : 0.91 (d, $J = 6.6$ Hz, 3H), 1.16 (d, $J = 6.6$ Hz, 3H), 1.98 (s, 3H), 2.11 (s, 3H), 3.05 (dd, $J_1 = 6.3$ Hz, $J_2 = 4$ Hz, 1H), 3.09 (s, 3H), 3.41 – 3.53 (m, 2H), 3.58 (s, 3H), 3.60 – 3.65 (m, 1H), 3.66 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 3.74 (s, 3H), 3.86 – 3.77 (m, 2H), 3.91 (d, $J = 7.6$ Hz, 1H), 4.02 (d, $J = 9.8$ Hz, 1H), 6.77 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 7.15 (d, $J = 8.6$ Hz, 2H), 7.26 (d, $J = 8.6$ Hz, 2H).

^{13}C δ : 9.54, 14.76, 34.54, 35.25, 49.48, 49.97, 51.57, 52.08, 52.31, 52.53, 53.06, 53.94, 55.32, 55.35, 55.55, 59.65, 61.84, 67.53, 69.28, 113.43, 113.99, 129.54, 129.70, 131.26, 132.60, 159.21, 159.40, 172.35, 173.53, 173.91, 173.99.

(\pm)-Dimethyl 2-benzyl-1-methyl-5-nonylpyrrolidine-3,4-dicarboxylate / (\pm)-dimethyl 2-benzyl-1-methyl-5-nonylpyrrolidine-3,4-dicarboxylate (259 + 260)



To a solution of *N*-methylphenylalanine (sodium chloride complex) (0.264 g, 1.110 mmol), and decanal (0.087 g, 0.555 mmol) in toluene (5 mL) was added dimethyl fumarate (0.0800 g, 0.555 mmol). The mixture was heated under reflux under Dean-Stark conditions for 16h, before being cooled. To the cooled solution was added 10 mL of saturated ammonium chloride solution and the organic layer separated. Extraction of the aqueous layer with (2 x 5 mL) ethyl acetate followed by combining of the organic layers, washing with water (1 x 5 mL), dried (Na_2SO_4) and concentration *in vacuo*, then purification through a bed of silica

gel with 50% ethyl acetate / hexanes led to 130 mg of an inseparable 1:1 mixture of diastereomers **259** and **260** (56%).

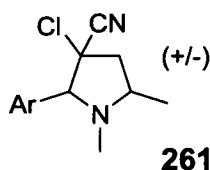
IR: 2926, 2855, 1736, 1458, 1437, 1204, 1174, 700.

MS (EI) m/z : 418 (9, $M+H^+$), 356 (34), 326 (32), 294 (30), 266 (73), 105 (79), 91 (100).

1H δ : 0.87 (t, $J = 6.3$ Hz, 6H), 1.24 – 1.53 (m, 32H), 2.31 (s, 3H), 2.37 (s, 3H), 2.48 – 2.67 (m, 2H), 2.78 - 2.88 (m, 2H), 3.02 – 3.21 (m, 4H), 3.35 (s, 3H), 3.47 (s, 3H), 3.51 – 3.66 (m, 4H), 3.68 (s, 3H), 3.70 (s, 3H), 7.13 – 7.28 (m, 10H).

^{13}C δ : 14.24 (2xC), 22.81 (2xC), 27.10, 28.34, 29.45, 29.48, 29.51, 29.65, 29.67, 29.71, 29.97, 30.05, 30.24, 32.02 (2xC), 33.61, 35.53, 35.63, 36.58, 48.82, 49.03, 50.24, 50.74, 51.64, 51.91, 52.18, 52.33, 64.55, 65.75, 66.56, 68.24, 126.15, 126.24, 128.32, 128.41, 129.15, 129.59, 138.80, 139.30, 171.89, 173.28, 174.22, 174.75. (1 carbon missing or overlapped).

(\pm)-3-Chloro-2-(4-methoxyphenyl)-1,5-dimethylpyrrolidine-3-carbonitrile (261**)**



To a solution of *N*-methylalanine (sodium chloride complex) (0.319 g, 1.976 mmol), and anisaldehyde (0.080 mL, 0.659 mmol) in toluene (4 mL) was added 2-chloroacrylonitrile (0.079 mL, 0.988 mmol). The mixture was heated under reflux under Dean-Stark conditions for 2h, before more 2-chloroacrylonitrile (0.079 mL, 0.988 mmol), was added. This was repeated after 4 hours of total reaction and the reaction allowed to reflux for another 16h before being cooled. To the cooled solution was added 10 mL of saturated ammonium chloride solution and the organic layer separated. Extraction of the aqueous layer with (2 x 5 mL) ethyl acetate followed by combining of the organic layers which were washed with

water (1 x 5mL) then dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography of the residue with neat dichloromethane as eluent yielded 104 mg of a 1:0.8:1 mixture of three diastereomers **261** (60%).

IR: 2926, 2214, 1611, 1516, 1254, 1181, 1030, 838, 736.

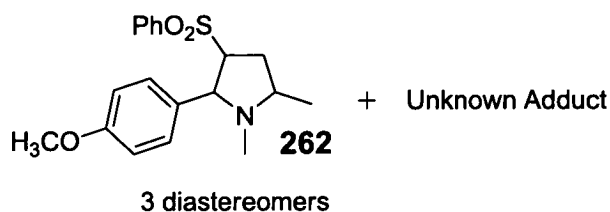
MS (EI) m/z : 264 (10%, M^+), 249 (4), 213 (16), 198 (9), 176 (100), 162 (26), 235 (16).

HRMS-EI m/z : 264.10290 [M] $^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{ClN}_2\text{O}$: 264.10294

^1H δ : 1.20 (d, $J = 6.6$ Hz, 3H), 1.26 (d, $J = 6.3$ Hz, 3H), 1.34 (d, $J = 6.4$ Hz, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 2.36-2.52 (m, 3H), 2.63 (s, 3H), 3.02 (dd, $J_1 = 14.2$, $J_2 = 10.6$ Hz, 1H), 3.12-3.24 (m, 2H), 3.54-3.72 (m, 3H), 3.94-3.99 (m, 3H), 6.88 (d, $J = 8.7$ Hz, 2H), 6.95 (d, $J = 8.7$ Hz, 2H), 7.25 (d, $J = 8.7$ Hz, 2H), 7.27 (d, $J = 8.7$ Hz, 2H), 7.36 (d, $J = 8.7$ Hz, 2H), 7.40 (d, $J = 8.7$ Hz, 2H).

^{13}C NMR δ : 9.94, 11.87, 15.94, 34.38, 34.81, 35.45, 40.90, 42.99, 48.95, 49.24, 55.45, 55.51, 55.60, 55.83, 61.26, 62.01, 64.96, 67.88, 69.42, 75.41, 76.89, 113.82, 114.09, 114.13, 114.22, 114.34, 114.57, 128.97, 129.30, 130.21, 130.32, 130.71, 132.21, 159.29, 159.57, 160.50.

(\pm)-2-(4-Methoxyphenyl)-1,5-dimethyl-3-(phenylsulfonyl)pyrrolidine (262**)**



To a solution of *N*-methylalanine (sodium chloride complex) (0.153 g, 0.945 mmol), and anisaldehyde (0.034 mL, 0.284 mmol) in toluene (4 mL) was added phenyl vinyl sulfone (0.032 g, 0.189 mmol). The mixture was heated under reflux under Dean-Stark conditions for 16h, before being cooled. To the cooled solution was added 10 mL of saturated

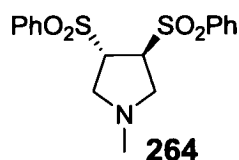
ammonium chloride solution and the organic layer separated. Extraction of the aqueous layer with (2 x 5 mL) ethyl acetate followed by combining of the organic layers which were washed with water (1 x 5 mL) then dried (Na_2SO_4) and concentrated *in vacuo*.

Chromatography of the residue with a gradient elution of neat CH_2Cl_2 , followed by 1% MeOH in CH_2Cl_2 , then 3% MeOH in CH_2Cl_2 yielded 0.065 mg of a mixture containing three diastereomers of **262** and an unknown adduct which GC/MS indicated consisted of 60% of the mixture.

Unknown adduct ^1H NMR data:

^1H NMR δ : 2.10 (s, 3H), 2.73 – 2.83 (m, 2H), 3.25 – 3.28 (m, 2H), 3.77 (s, 3H), 6.78 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.50 – 7.68 (m, 6H), 7.82 – 7.91 (m, 4H).

(\pm)-(3*R*,4*R*)-1-Methyl-3,4-bis(phenylsulfonyl)pyrrolidine (264**)**



1,2-*trans*-Bisphenylsulfonyl ethylene (98.5 mg, 0.32 mmol), sarcosine (85.0 mg, 0.96 mmol) and paraformaldehyde (48.0 mg, 1.60 mmol) were heated under Dean-Stark conditions in toluene (10 mL) for 3 hours. After this time the reaction was cooled, and washed with water (2 x 10 mL), then dried (Na_2SO_4). Evaporation yielded 115 mg of an off-white solid (>95% yield).

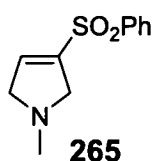
IR: 689, 729, 1084, 1150, 1310, 1447, 2794, 2958.

MS (EI) m/z : 366(4%, M^+), 224 (8), 125 (8), 83 (14), 82(100), 67 (9).

HRMS-EI m/z : 365.0747 [M] $^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_4\text{S}_2$:. 365.0755

^1H δ :	2.32 (s, 3H), 2.92 (dd, $J_1 = 10.2$ Hz, $J_2 = 7.2$ Hz, 2H), 3.07 (dd, $J_1 = 10.2$ Hz, $J_2 = 4.5$ Hz, 2H), 4.08 – 4.14 (m, 2H), 7.53 – 7.58 (m, 4H), 7.65 – 7.71 (m, 2H), 7.79 – 7.83 (m, 3H).
^{13}C δ :	41.40 (CH ₃), 56.40 (CH ₂), 64.07 (CH), 128.75 (CH), 129.58 (CH), 134.46 (CH), 137.70 (C)

1-Methyl-3-(phenylsulfonyl)-2,5-dihydro-1H-pyrrole (265)



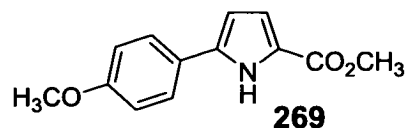
To a stirred solution of 1-methyl-3,4-bis(phenylsulfonyl)pyrrolidine (0.035 g, 0.096 mmol) in dichloromethane / methanol (10 mL, 1:1), was added NaOMe (0.016 g, 0.287 mmol). The reaction was left to stir for 60 min, before the addition of 10 mL of saturated ammonium chloride. A further 10 mL of dichloromethane was added before the organic layer was separated and washed with water (2 x 10 mL), then dried (Na₂SO₄). Concentration under reduced pressure yielded 6 mg of **241** as a yellow oil (28%).

MS (EI) m/z : 223(19%, M⁺), 158(8), 125 (10), 114 (18), 96 (14), 81 (100), 71 (32), 42 (33).

HRMS-EI m/z : 223.06655 [M]⁺ calcd for C₁₁H₁₃NO₂S: 223.06670

^1H δ : 2.42 (s, 3H), 3.59 – 3.66 (m, 4H), 6.74 (m, 1H), 7.52 – 7.66 (m, 3H), 7.87 – 7.91 (m, 2H).

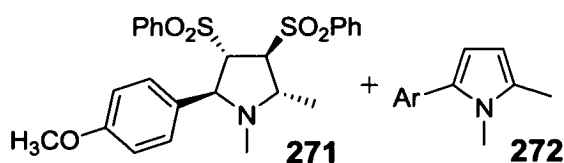
^{13}C δ : 42.27, 59.35, 61.90, 127.98, 128.53, 129.43, 130.81, 129.64, 142.47.

Methyl 5-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (269)

Imine **165** (0.119 g, 0.573 mmol) was dissolved in acetonitrile (10 mL) and silver acetate (0.146 g, 0.859 mmol), and DBU (0.086 mL, 0.573 mmol) were added. To this solution was added *trans*-1,2-bis-phenylsulfonyl ethylene (0.177 g, 0.573 mmol) and the reaction stirred for 20h. After reaction saturated ammonium chloride solution (10 mL) was added, and the mixture extracted with TBME (3 x 8 mL). The combined organic extracts were washed with brine (2 x 5 mL) and dried (Na₂SO₄). Concentration under reduced pressure yielded a residue which was subjected to flash chromatography on silica with 3% MeOH in CH₂Cl₂ as eluent to yield 22 mg of **269** as a light yellow oil (17%).

¹H δ: 3.83 (s, 3H), 3.86 (s, 3H), 6.42-6.45 (m, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 7.52 (d, *J* = 8.9Hz, 2H), 9.52 (bs, 1H).

(±)-(2*R*,3*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-1,5-dimethyl-3,4-bis(phenylsulfonyl)pyrrolidine (271)



To a solution of *N*-methylalanine (sodium chloride complex) (0.594 g, 3.68 mmol) and anisaldehyde (0.151 mL, 1.112 mmol) in *m*-xylene was added *trans*-1,2-bisphenylsulfonyl ethylene (284 mg, 0.921 mmol). The mixture was heated under Dean-Stark reflux conditions for 16h, before being cooled and washed with saturated ammonium chloride, dried (Na₂SO₄), and concentrated *in vacuo*. Chromatography (20% ethyl acetate in

hexanes) yielded 308 mg (69% yield) of the title pyrrolidine **271** as a colourless solid, as well as pyrrole **272** (2-(4-methoxyphenyl)-1,5-dimethylpyrrole) in 7% yield (13.5 mg).

(±)-(2*R*,3*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-1,5-dimethyl-3,4-bis(phenylsulfonyl)pyrrolidine

271:

IR: 1512, 1448, 1310, 1249, 1148, 1079, 687.

MS (EI) *m/z*: 341 (12), 202 (100), 187 (20), 125 (9), 77 (14).

HRMS APCI *m/z*: 486.1408, [M+H]⁺ calcd for C₂₅H₂₇NO₅S₂ 486.1403.

¹H δ: 1.16 (d, *J* = 6.8 Hz, 3H), 2.01 (s, 3H), 3.71 (s, 3H), 3.73 – 3.87 (m, 2H), 3.98 – 4.12 (m, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.29 – 8.10 (m, 10H).

¹³C δ: 14.33, 34.80, 55.34, 58.90, 65.57, 67.02, 68.46, 113.79, 128.61, 128.69, 128.80, 129.08, 129.25, 134.08, 134.18, 134.29, 138.49, 139.69, 159.32.

2-(4-Methoxyphenyl)-1,5-dimethyl-pyrrole **272:**

IR: 2913, 1607, 1512, 1249, 1175, 1031, 835.

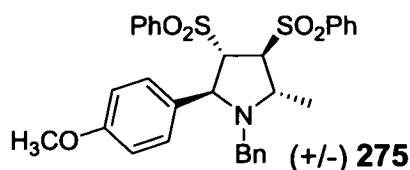
MS (EI) *m/z*: 201(66%, M⁺), 186 (76), 135(100), 122(26), 107 (33), 91 (28), 77(36), 49 (67).

HRMS-EI *m/z*: 201.11521 [M]⁺ calcd for C₁₃H₁₅NO: 201.11536.

¹H δ: 2.30 (s, 3H), 3.48 (s, 3H), 3.84 (s, 3H), 5.95 (d, *J* = 3.7 Hz, 1H), 6.06 (d, *J* = 3.7 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H).

¹³C δ: 13.02, 31.79, 55.53, 106.22, 106.87, 113.98, 126.82, 127.14, 130.32, 144.13, 158.67.

(±)-(2*R*,3*R*,4*R*,5*R*)-1-Benzyl-2-(4-methoxyphenyl)-5-methyl-3,4-bis(phenylsulfonyl)pyrrolidine (275)



To a solution of *N*-benzylalanine sodium chloride complex (0.680 g, 2.86 mmol) and anisaldehyde (0.156 g, 1.144 mmol) in *m*-xylene was added *trans*-1,2-bisphenylsulfonylethylene (0.294 g, 0.953 mmol). The mixture was heated under Dean-Stark reflux conditions for 16h before being cooled and washed with saturated ammonium chloride, dried (Na₂SO₄), and concentrated *in vacuo*. Chromatography (20% ethyl acetate in hexanes) yielded 0.285 g (53% yield) of the title pyrrolidine as a colourless solid. Crystals suitable for X-ray crystallography were grown from ethyl acetate / hexanes.

IR: 1611, 1512, 1447, 1309, 1248, 1151, 1031, 836, 748.

MS (EI)*m/z*: 561(1%, M⁺), 546(10), 446 (12), 420 (12), 326 (10), 278 (100), 186 (50), 91 (95).

HRMS-EI *m/z*: 561.16717 [M]⁺ calcd for C₃₁H₃₁NO₅S₂:. 561.16436

¹H δ: 1.09 (d, *J* = 6.6 Hz, 3H), 3.27 (d, *J* = 13.8 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.78 - 3.85 (m, 2H), 3.80 (s, 3H), 4.22 (dd, *J*₁ = 7.2 Hz, *J*₂ = 3.6 Hz, 1H), 4.30 (d, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 9 Hz, 2H), 7.17 - 7.32 (m, 6H), 7.42 - 7.78 (m, 11H).

¹³C δ: 12.50 (CH₃), 49.95 (CH₂), 55.03 (CH), 55.38 (CH₃), 65.72 (CH), 69.34 (CH), 70.51 (CH), 114.02 (CH), 127.22 (CH), 128.45 (CH), 128.82 (CH), 129.10 (CH), 129.33 (CH), 129.57 (CH), 131.69 (C), 134.29 (CH), 137.69 (C), 137.96 (C), 159.51 (C). (4 carbons missing or overlapped).

Formula C₃₁H₃₁NO₅S₂ ***M*** 561.69 **Crystal system** triclinic **Space group** *P*-1

a (Å) 9.971(4) b (Å) 10.4100(16) c (Å) 13.903(13)

α (°) 84.25(4) β (°) 84.74(6) γ (°) 78.55(2)

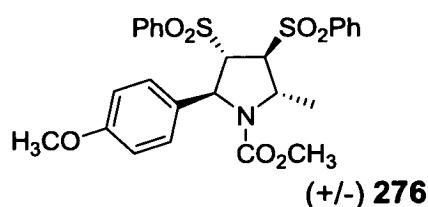
U (Å³) 1403.5(15) D_{calc} (g cm⁻³) 1.329 $Z = 2$

μ (mm⁻¹) 0.231 **Specimen** (mm) 0.52x0.38x0.35

$2\theta_{\text{max}}$ (°) 50.0 N_t 5157 $N(R_{\text{int}})$ 4932(0.0253) N_o 4169

R 0.0577 R_w 0.1711 **GOOF** 1.045

(±)-(2*R*,3*R*,4*R*,5*R*)-Methyl 2-(4-methoxyphenyl)-5-methyl-3,4-bis(phenylsulfonyl)pyrrolidine-1-carboxylate (276)

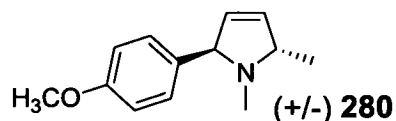


Pyrrolidine **275** (47.0 mg, 0.0840 mmol) was hydrogenated under 1 atmosphere of hydrogen over 10% palladium on carbon (5 mg) in methanol for 16h. The reaction was filtered through Celite, and then concentrated under vacuum. The concentrate was dissolved in CH₂Cl₂ (3 mL), then 0.10 g (ca. 15 eq) of sodium bicarbonate and 0.10 mL (ca. 15eq) of methyl chloroformate were added. The suspension was stirred for 23h, before more CH₂Cl₂ was added (5 mL), and organic phase was washed with water (3 x 5 mL), then dried (Na₂SO₄). Concentration *in vacuo*, followed by silica gel chromatography (30% ethyl acetate in hexanes) gave 38 mg of the carbamate **276** as a clear oil (87% yield), present as a 3:2 mix of rotamers as determined by ¹H NMR spectra.

IR: 700, 763, 1034, 1172, 1249, 1379, 1436, 1512, 1611, 1733 (C=O), 2836, 2952.

^1H δ :	0.900 (d, J = 6.6 Hz, 1.8H), 1.112 (d, J = 6.6 Hz, 1.2H), 3.03 - 3.06 (m, 0.5H), 3.28 - 3.43 (m, 1H), 3.49 - 3.63 (m, 1.5H), 3.653 (s, 1.8H), 3.726 (s, 1.2H), 3.784 (s, 1.8H), 3.791 (s, 1.2H), 3.80 - 3.86 (m, 1H), 4.065 (d, J = 7.5Hz, 0.6H), 4.260 (d, J = 9.6 Hz, 0.4H), 6.83 - 6.90 (m, 2H), 7.21 - 7.41 (m, 12H).
^{13}C δ :	8.94 (CH ₃), 13.90 (CH ₃), 49.14 (CH), 49.36 (CH), 51.36 (CH), 51.51 (CH), 51.94 (CH ₃), 52.70 (CH ₃), 54.21 (CH), 54.86 (CH), 55.31 (CH ₃), 55.31 (CH ₃), 65.81 (CH) 67.59 (CH), 159.29 (C), 159.22 (C), 172.38 (C=O), 172.28 (C=O), 139.27 (C), 139.97 (C), 133.38 (C), 131.64 (C), 113.42 (CH), 114.01 (CH), 126.77 (CH), 127.01 (CH), 128.04 (CH), 128.28 (CH), 128.35 (CH), 128.45 (CH), 129.32 (CH), 129.80 (CH). The rest obscured!

(\pm)-(2*S*,5*R*)-2-(4-Methoxyphenyl)-1,5-dimethyl-2,5-dihydro-1*H*-pyrrole (280**)**



To a solution of (\pm)-(2*R*,3*R*,4*R*,5*R*)-2-(4-methoxyphenyl)-1,5-dimethyl-3,4-bis(phenylsulfonyl)pyrrolidine (0.0262 g, 0.054 mmol) in methanol (3 mL) was added magnesium turnings (0.0260 g, 1.079 mmol), and mercuric chloride (5 mg, cat.). The mixture was sonicated for 1h, before being washed with 0.5M sodium carbonate (10 mL) and extracted with ethyl acetate (3 x 7 mL). Concentration under reduced pressure yielded 0.010 g of (\pm)-(2*S*,5*R*)-2-(4-methoxyphenyl)-1,5-dimethyl-2,5-dihydro-1*H*-pyrrole (**280**), 91% yield.

IR: 833, 1037, 1174, 1245, 1511, 1609, 2961.

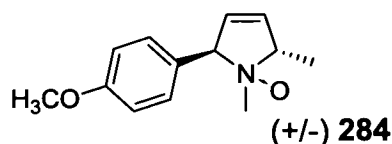
MS (EI) m/z : 203(14%, M^+), 188 (100), 173 (23), 160 (42), 150(77), 121 (52), 105 (38), 58 (47).

HRMS EI m/z : 203.13022 [M] $^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{NO}$:. 203.13101

^1H δ : 1.196 (d, J = 6.6 Hz, 3H), 2.192 (s, 3H), 3.798 (s, 3H), 3.863 – 3.890 (m, 1H), 4.708 – 4.723 (m, 1H), 5.774 – 5.794 (m, 1H), 5.901 – 5.921 (m, 1H), 6.861 (d, J = 9.6 Hz, 2H), 7.152 (d, J = 9.6 Hz, 2H).

^{13}C : 17.320 (CH₃), 34.670 (CH₃), 55.391 (CH₃), 64.799 (CH), 73.219 (CH), 113.804 (CH), 129.073 (C), 129.650 (CH), 131.586 (CH), 134.001 (CH), 159.20 (C).

(±)-(2*S*,5*R*)-2-(4-Methoxyphenyl)-1,5-dimethyl-2,5-dihydro-1*H*-pyrrole-*N*-oxide (284)



To a solution of **280** (0.010 g, 0.049 mmol) in CH₂Cl₂ (3 mL) was added TFA (0.005 mL, 0.074 mmol) followed by *m*-CPBA (0.042 g, 0.246 mmol). The reaction was stirred for 16h before being quenched with saturated sodium sulfite solution (5 mL). 2M sodium carbonate was added (2 mL) and the mixture extracted with CH₂Cl₂ (2 x 4 mL). The combined organic extracts were dried (Na₂SO₄), filtered then concentrated *in vacuo* to yield 10 mg of a clear oil (>95%).

IR: 2932, 1696, 1610, 1513, 1382, 1253 (S), 1178, 1031, 835, 755.

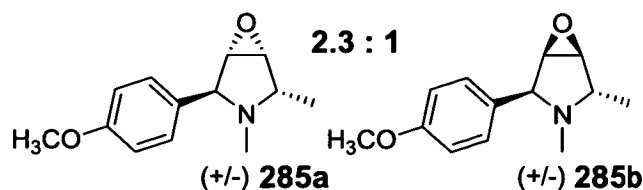
MS (EI) m/z : 220 (2, $\text{M}+\text{H}^+$), 201 (21), 186 (24), 174 (100), 159 (55), 139 (37), 111 (21).

HRMS APCI m/z : 220.1335, $[\text{M}+\text{H}]^+$ calcd for C₁₃H₁₇NO₂: 220.1337.

^1H δ : 1.63 (d, J = 6.8 Hz, 3H), 3.00 (s, 3H), 3.83 (s, 3H), 4.49 – 4.64 (m, 1H), 6.09 – 6.19 (m, 3H), 6.83 – 6.93 (m, 1H), 6.96 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H).

^{13}C δ : 13.09, 50.36, 55.54, 78.12, 87.45, 114.92, 127.94, 129.38, 130.87, 131.60, 161.66.

((±)- (1S,2S,4S,5R)-2-(4-Methoxyphenyl)-3,4-dimethyl-6-oxa-3-azabicyclo[3.1.0]hexane /
 (±)-(1R,2S,4S,5S)-2-(4-methoxyphenyl)-3,4-dimethyl-6-oxa-3-azabicyclo[3.1.0]hexane)
 (285a + 285b)



To a solution of (±)-(2S,5R)-2-(4-methoxyphenyl)-1,5-dimethyl-2,5-dihydro-1H-pyrrole (18.3 mg, 0.090 mmol), in TFA (3mL) was added sodium percarbonate (87 mg, 0.36 mmol). The reaction was stirred for 3 h, before being quenched by the addition of water 2mL, and sodium sulfite (0.5 g). The TFA was removed *in vacuo*, then 5 mL of 2M Na₂CO₃ was added, then the aqueous was extracted with ethyl acetate (4 x 5 mL), and the combined organic extracts were dried with Na₂SO₄. Concentration under reduced pressure yielded 12.4 mg (63%) of two diastereomers (**285a** and **285b**) as an oil which was carried through without purification.

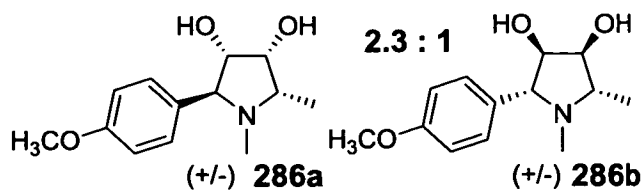
MS (EI) *m/z*: 219(38%, M⁺), 204 (78), 176 (37), 148 (100), 121(52), 84 (36), 69 (49), 51 (47).

HRMS-EI *m/z*: 219.12566 [M]⁺ calcd for C₁₃H₁₇NO₂:. 219.12593

¹H δ: 1.02 (d, *J* = 6.3 Hz, 0.9H), 1.25 (d, *J* = 6.3 Hz, 2.1 H), 2.03 (s, 2.1H), 2.15 (s, 0.9H), 2.93 – 3.00 (m, 1H), 3.56 – 3.61 (m, 1H), 3.72 – 3.74 (m, 1H), 3.81 – 3.89 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 1.4H), 7.07 (d, *J* = 8.7 Hz, 1.4H), 7.36 (d, *J* = 8.7 Hz, 0.6H), 7.65 (d, *J* = 8.7 Hz, 0.6H).

¹³C NMR: (Major diastereomer only) 11.46, 34.52, 55.32, 55.60, 57.84, 61.24, 67.01, 115.44, 127.48, 129.53, 159.25.

(±)-3,4-Epi and 4,5-epicodonopsinine (**286a** + **286b**)

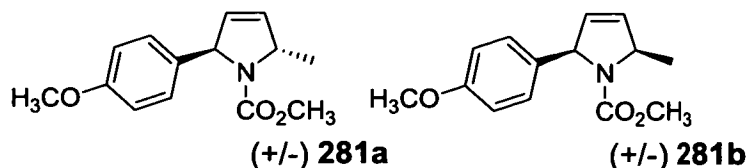


To a mixture of diastereomeric epoxides **285a** and **285b** (18.3 mg, 0.083 mmol), in 1,4-dioxane (2 mL), was added 3M sulfuric acid (0.278 mL, 0.835 mmol). The reaction mixture was heated under reflux for 5h, then returned to room temperature, before the dioxane was removed *in vacuo*. 2M sodium hydroxide (3 mL, and sodium bicarbonate (0.3 g) were added, and the aqueous was extracted with ethyl acetate (5 x 4 mL). The combined organic extracts were dried (Na_2SO_4), then condensed under reduced pressure. Flash chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1) led to 11.4 mg (58%), of a 2.3:1 diastereomeric mixture of isomers of codonopsinine.

MS (EI) m/z : 238 ($\text{M}+\text{H}^+$, 4), 219 (48), 204 (78), 186 (52), 176 (39), 148 (100), 121 (51), 77 (54).

^1H δ (D_5 Pyridine): 0.86 (d, J = 6.8 Hz, 0.9H), 1.23 (d, J = 6.1 Hz, 2.1H), 2.03 (s, 2.1H), 2.09 (s, 0.9H), 2.90 – 2.99 (m, 0.7H), 3.44 – 3.54 (m, 0.7H), 3.56 – 3.66 (m), 3.66 (s, 0.9H), 3.70 (s, 2.1H), 3.73 – 3.78 (m), 3.90 – 4.13 (m), 4.34 – 4.36 (m, 0.7 H), 7.01 (d, J = 8.6 Hz, 0.6H), 7.02 (d, J = 8.6 Hz, 1.4 H), 7.12 (d, J = 8.7 Hz, 1.4 H), 7.61 (d, J = 8.7 Hz, 0.6 H).
(Not all integrals were clear where diastereomeric resonances were overlapping).

^{13}C δ (D_5 Pyridine): 9.00, 12.94, 31.80, 32.79, 53.72, 55.48, 56.38, 57.02, 57.10, 58.94, 60.09, 63.87, 64.83, 65.70, 112.67, 112.90, 128.16, 128.60, 128.63, 129.33, 158.17, 158.35.

Methyl 2-(4-methoxyphenyl)-5-methyl-2,5-dihydro-1H-pyrrole-1-carboxylate**(2:1 mixture of 281a : 281b)**

To a solution of (±)-(2*R*,3*R*,4*R*,5*R*)-methyl 2-(4-methoxyphenyl)-5-methyl-3,4-bis(phenylsulfonyl)pyrrolidine-1-carboxylate (66 mg, 0.125 mmol), in methanol was added acid washed magnesium turnings (61 mg, 2.492 mmol) and mercuric chloride (1 mg). The mixture was sonicated for 1h before being concentrated *in vacuo*. The residue was then added to 2M sodium carbonate (5 mL) before being extracted with ethyl acetate (3 x 5 mL). It was then dried and concentrated before silica gel chromatography (eluent 20% ethyl acetate in hexanes) yielded 10 mg (33% yield) of the title compound being a mixture of rotameric diastereomers **281a** and **281b** as a clear oil.

IR: 831, 1033, 1112, 1176, 1247, 1378, 1445, 1512, 1611, 1694 (C=O), 2955.

MS (EI)*m/z*: 247(28%, M^+), 232 (78), 200 (42), 190 (100), 172(46), 159 (40), 144 (32), 91 (93).

HRMS-EI *m/z*: 247.12079 [M]⁺ calcd for C₁₄H₁₇NO₃: 247.12048

(281a):

¹H δ: 1.359 (d, *J* = 6.3 Hz, 1.4H), 1.435 (d, *J* = 6 Hz, 1.6H), 3.424 (s, 1.6H), 3.630 (s, 1.4H), 3.771 (s, 1.4 H), 3.787 (s, 1.6H), 4.73 - 4.78 (m, 0.5H), 4.82 - 4.87 (m, 0.5H), 7.177 (d, *J* = 8.7 Hz, 1H), + *cis* overlapped.

(281b):

¹H δ: 1.230 (d, *J* = 6.6 Hz, 1.4H), 1.296 (d, *J* = 6.3 Hz, 1.6H), 3.492 (s, 1.6 H), 3.684 (s, 1.4H), 4.16 - 4.21 (m, 0.4H), 4.24 - 4.29 (m, 0.6H), 7.085 (d, *J* = 8.7 Hz,

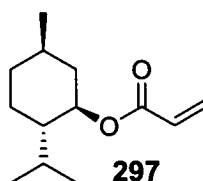
1H) + *trans* overlapped. (Methyl of the carbamate obscured at 3.7-3.8 ppm)

(281a + 281b):

^1H δ : 5.38 – 5.41 (m, 1H), 5.45 – 5.49 (m, 1H), 5.58 – 5.65 (m, 2H), 5.75 – 5.79 (m, 2H), 6.80 – 6.86 (m, 6H).

^{13}C δ : 19.90, 21.06, 52.00, 52.28, 60.51, 61.18, 68.00, 68.35, 113.81, 113.95, 126.28, 126.52, 127.91, 128.39, 130.66, 130.87, 133.30, 134.25, 158.94, 159.08. (Carbamate not observed due to fluctuonality.) (Only *Trans* rotamers observed.)

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl acrylate (297)



To a stirred cooled (0°C) solution of L - menthol (13.393 g, 86 mmol), in dichloromethane (200 mL) was added dimethylamino pyridine (0.01 g), acryloyl chloride (10.40 mL, 129 mmol) and triethylamine (17.92 mL, 129 mmol). The solution was allowed to warm to room temperature (20°C) and was stirred for 16h. The solution was washed with water (3 x 50 mL), dried (MgSO₄) and filtered through a bed of silica (eluent 10% ethyl acetate in hexanes). The organic solvent was removed to yield 12.09 g (67%) of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexylacrylate.

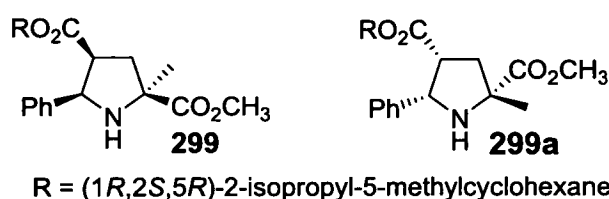
IR: 984, 1047, 1181, 1196, 1269, 1295, 1720 (C=O), 2928, 2956.

^1H δ : 0.755 (d, J = 6.9 Hz, 3H), 0.891 (m, 6H), 0.93 – 1.09 (m, 3H), 1.36 – 1.56 (m, 2H), 1.65 – 1.72 (m, 2H), 1.81 – 1.92 (m, 1H), 1.98 – 2.06 (m, 1H), 4.752 (ddd, $J_1 = J_2 = 10.8$ Hz, $J_3 = 4.2$ Hz, 1H), 5.790 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.5$ Hz,

1H), 6.095 (dd, $J_1 = 17.1$ Hz, $J_2 = 10.2$ Hz, 1H), 6.376 (dd, $J_1 = 17.1$ Hz, $J_2 = 1.5$ Hz, 1H).

^{13}C δ : 16.53 (CH₃), 20.86 (CH₃), 22.16 (CH₃), 23.64 (CH₂), 26.43 (CH), 31.51 (CH), 34.38 (CH₂), 40.99 (CH₂), 47.20 (CH), 74.46 (CH), 129.16 (CH), 130.39 (CH₂), 166.00 (C=O).

(2*S*,4*S*,5*R*)-4-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-methyl 2-methyl-5-phenylpyrrolidine-2,4-dicarboxylate / (2*R*,4*R*,5*S*)-4-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-methyl 2-methyl-5-phenylpyrrolidine-2,4-dicarboxylate (299 + 299a)



To a solution of (*E*)-methyl 2-(benzylideneamino)propanoate (0.0742 g, 0.388 mmol) in dry acetonitrile (15 mL) under nitrogen, was added silver acetate (0.097 g, 0.582 mmol) and DBU (58.0 μL , 0.388 mmol). To the vigorously stirred suspension was added menthyl acrylate (0.163 g, 0.776 mmol). The reaction was protected from light and stirred for 16h, after which it was quenched by the addition of saturated ammonium chloride solution (10 mL), and extracted with *t*-butyl methyl ether (3 x 10 mL). After drying (Na_2SO_4) and concentration under reduced pressure, column chromatography with 20% ethyl acetate in hexanes to 50% ethyl acetate in hexanes yielded 0.1012 g of a mixture of two diastereomers of product as a clear oil. (65% yield.)

299:

IR: 699, 1139, 1192, 1244, 1373, 1447, 1729 (C=O), 2955.

^1H δ : 0.53 (d, $J = 7.2$ Hz, 3H), 0.68 (d, $J = 6.6$ Hz, 3H), 0.75 (d, $J = 7.2$ Hz, 3H), 0.81 – 1.22 (m, 9H), 1.472 (s, 3H), 2.06 (dd, $J_1 = 13.8$ Hz, $J_2 = 7.8$ Hz, 1H), 2.65 (dd, J_1

= 13.8 Hz, J_2 = 4.8 Hz, 1H), 3.29 – 3.36 (m, 1H), 3.771 (s, 3H), 4.31 (ddd, J_1 = J_2 = 11.1 Hz, J_3 = 4.5 Hz, 1H), 4.586 (d, J = 7.2 Hz, 1H), 7.17 – 7.30 (m, 5H).

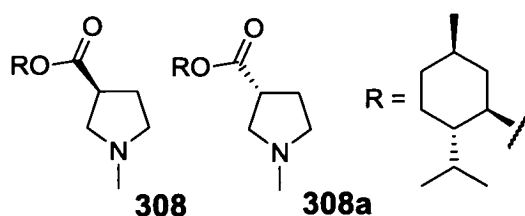
^{13}C δ : 16.052 (CH₃), 20.782 (CH₃), 21.807 (CH₃), 23.113 (CH₂), 25.930 (CH), 27.548 (CH₃), 31.025 (CH), 34.017 (CH₂), 39.689 (CH₂), 41.397 (CH₂), 46.538 (CH), 50.167 (CH), 52.521 (CH₃), 64.692 (CH), 65.733 (C), 74.024 (CH), 127.091 (CH), 127.425 (CH), 128.276 (CH), 138.952 (C), 172.467 (C=O), 176.468 (C=O).

299a:

^1H δ : All peaks overlap with **299**.

^{13}C δ : 15.763, 20.980, 21.898, 22.779, 25.300, 27.737, 31.162, 40.380, 41.640, 46.393, 50.797, 64.578, 65.634, 74.161, 126.795, 127.357, 128.048, 138.701, 172.292, 176.355, 2 resonances overlapped or missing.

(*S*)-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 1-methylpyrrolidine-3-carboxylate / (*R*)-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 1-methylpyrrolidine-3-carboxylate (**308** + **308a**)



A solution of sarcosine (0.113 g, 1.267 mmol), paraformaldehyde (0.152 g, 5.070 mmol) and menthol acrylate (0.133 g, 0.633 mmol) were heated under reflux in toluene (5 mL) under Dean-Stark conditions for 16h. After cooling, ethyl acetate (10 mL) was added and the organic layers were washed with water (3 x 5 mL) and dried (Na₂SO₄). Concentration *in vacuo*, followed by purification through a plug of silica with 20% ethyl acetate in hexanes

followed by DCM/MeOH/NH₃ (80:19:1) as eluent yielded an inseparable approximately 1:1 mixture of diastereomers **308** and **308a** as 67 mg of clear oil (40%).

IR: 3423, 2956, 1729, 1455, 1370, 1190, 1173, 1039, 985.

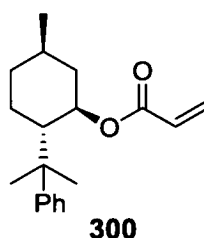
MS (EI) *m/z*: 267 (8%, M⁺), 128 (100), 112 (7), 83 (7).

HRMS-EI *m/z*: 267.21974 [M]⁺ calcd for C₁₆H₂₉NO₂: 267.21983.

¹H δ: 0.70 (d, *J* = 7.0 Hz, 3H), 0.82 – 0.87 (m, 6H), 0.88 – 1.05 (m, 2H), 1.27 – 1.53 (m, 2H), 1.57 – 1.69 (m, 2H), 1.74 – 1.84 (m, 1H), 1.87 – 1.96 (m, 1H), 2.00 – 2.16 (m, 2H), 2.36 (s, 3H), 2.43 – 2.53 (m, 1H), 2.56 – 2.63 (m, 1H), 2.66 – 2.74 (m, 1H), 2.87 – 3.07 (m, 2H), 4.62 (ddd, *J*₁ = *J*₂ = 10.8 Hz, *J*₃ = 4.4 Hz, 1H).

¹³C δ: 16.31, 16.33, 20.90 (2xC), 22.13 (2xC), 23.42 (2xC), 26.31 (2xC), 28.42, 28.45, 31.45 (2xC), 34.34 (2xC), 40.91, 40.94, 41.98 (2xC), 42.88, 42.94, 47.05, 47.07, 56.07, 56.13, 58.90, 58.91, 74.42, 74.45, 174.56 (2xC).

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexylacrylate (300**)**



To a stirred, cooled (0°C), solution of (-)-8-phenylmenthol (1.3189 g, 5.68 mmol) (prepared by undergraduate students by the method of Ort¹⁹³), in dichloromethane (40 mL) was added dimethylaminopyridine (0.01 g), acryloyl chloride (0.918 mL, 11.35 mmol) and triethylamine (1.582 mL, 11.35 mmol). The solution was allowed to warm to room temperature (20°C) and was stirred for 16h. The solution was washed with water (3 x 20 mL), dried (MgSO₄) and filtered through a bed of silica (eluent 10% ethyl acetate in

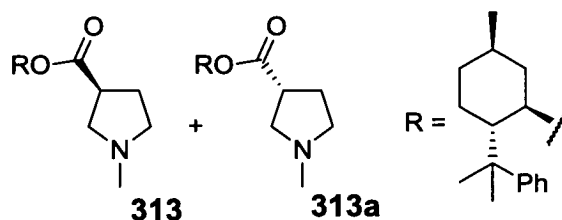
hexanes). The organic solvent was removed to yield 1.154 g (71%) of (1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl acrylate.

IR: 700, 1201, 1271, 1296, 1405, 1717 (C=O), 2923, 2954.

^1H δ : 0.866 (d, $J = 6.6$ Hz, 3H), 0.92 – 1.13 (m, 2H), 1.22 (s, 3H), 1.30 (s, 3H), 1.42 – 1.55 (m, 2H), 1.61 – 1.70 (m, 2H), 1.88 – 1.95 (m, 1H), 2.00 – 2.09 (m, 1H), 4.86 (ddd, $J_1 = J_2 = 10.8$ Hz, $J_3 = 4.2$ Hz, 1H), 5.55 – 5.59 (m, 2H), 5.97 – 6.05 (m, 1H), 7.08 – 7.13 (m, 1H), 7.22 – 7.28 (m, 4H).

^{13}C δ : 21.94 (CH₃), 25.50 (CH₃), 26.77 (CH₃), 27.71 (CH₂), 31.44 (CH), 34.72 (CH₂), 39.86 (C), 41.77 (CH₂), 50.67 (CH), 74.70 (CH), 125.12 (CH), 125.55 (CH), 128.12 (CH₂), 129.03 (CH), 130.08 (CH), 151.72 (C), 165.58 (C=O).

(*S*)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-methylpyrrolidine-3-carboxylate / (*R*)-((1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-methylpyrrolidine-3-carboxylate



A solution of sarcosine (0.055 g, 0.618 mmol), paraformaldehyde (0.037 g, 1.236 mmol) and (-)-8-phenylmenthol acrylate (0.0354 g, 0.124 mmol) were heated under reflux in toluene (3 mL) under Dean-Stark conditions for 16h. After cooling, ethyl acetate (10mL) was added and the organic layers were washed with water (3 x 5 mL) and dried (Na₂SO₄).

Concentration *in vacuo*, followed by purification through a plug of silica with a DCM/MeOH/NH₃ (80:19:1) eluent yielded 19mg of an inseparable mixture of diastereomers **313** and **313a** in a 1:2 ratio as a clear oil (45%).

IR: 2955, 1725, 1444, 1188, 1173, 1092, 1005, 765, 701.

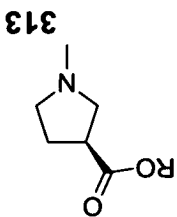
MS (EI) m/z : (66%, M^+), (76), 135(100), 122(26), 107 (33), 91 (28), 77(36), 49 (67).

The ^1H NMR spectrum appears as only one compound, both diastereomers are overlapped.

^1H δ : 0.86 (d, J = 6.4 Hz, 3H), 1.10 – 1.23 (m, 2H), 1.18 (s, 3H), 1.28 (s, 3H), 1.40 – 1.51 (m, 2H), 1.62 – 1.84 (m, 3H), 1.92 – 2.08 (m, 2H), 2.20 – 2.31 (m, 2H), 2.38 (s, 3H), 2.45 – 2.55 (m, 2H), 2.78 – 3.02 (m, 2H), 4.80 (ddd, $J_1 = J_2 = 10.6$ Hz, $J_3 = 4.2$ Hz, 1H), 7.09 – 7.15 (m, 2H), 7.23 – 7.28 (m, 3H).

^{13}C δ : 22.01 (both), 23.86 (minor), 24.36 (major), 26.56 (minor), 26.66 (major), 27.49 (both), 28.88 (minor), 28.94 (major), 29.29 (both), 31.47 (minor), 31.49 (major), 34.67 (minor), 34.70 (major), 39.74 (minor), 39.79 (major), 41.44 (minor), 41.49 (major), 42.13 (minor), 42.43 (major), 50.36 (both), 54.97 (minor), 55.45 (major), 56.68 (minor), 57.89 (major), 74.87 (minor), 75.06 (major), 125.37 (major), 125.43 (minor), 125.53 (both), 128.11 (minor), 128.14 (major), 151.95 (minor), 151.97 (major), 173.33 (major), 173.44 (minor).

(S)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-methylpyrrolidine-3-carboxylate (**313**)



A solution of **313** and **313a** was heated in toluene (3 mL) with a catalytic amount of DBU (5 μL) for 16h under Dean-Stark conditions. After cooling 5 mL of ethyl acetate was added,

and the organic layer was washed with water (2 x 5 mL), dried (Na₂SO₄) and concentrated *in vacuo* to yield **313**.

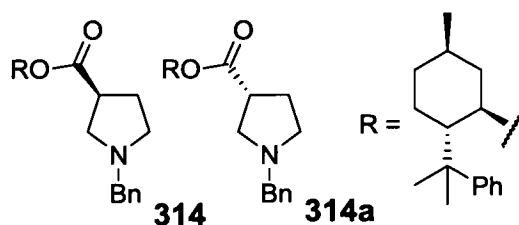
MS (EI) *m/z*: 343(10%, M⁺), 128 (100), 91(8).

HRMS-EI *m/z*: 343.25109 [M]⁺ calcd for C₂₂H₃₃NO₂: 343.25113.

¹H δ: 0.86 (d, *J* = 6.4 Hz, 3H), 1.10 – 1.23 (m, 2H), 1.18 (s, 3H), 1.28 (s, 3H), 1.40 – 1.51 (m, 2H), 1.62 – 1.84 (m, 3H), 1.92 – 2.08 (m, 2H), 2.20 – 2.31 (m, 2H), 2.38 (s, 3H), 2.45 – 2.55 (m, 2H), 2.78 – 3.02 (m, 2H), 4.80 (ddd, *J*₁ = *J*₂ = 10.6 Hz, *J*₃ = 4.2 Hz, 1H), 7.09 – 7.15 (m, 2H), 7.23 – 7.28 (m, 3H).

¹³C δ: 21.40, 24.66, 26.58, 27.36, 28.87, 29.41, 31.33, 34.61, 39.68, 41.65, 42.55, 50.36, 55.96, 58.11, 74.30, 125.13, 125.40, 127.92, 151.76, 174.28.

(S)-((1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-benzylpyrrolidine-3-carboxylate / (R)-((1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-benzylpyrrolidine-3-carboxylate (314** + **314a**)**



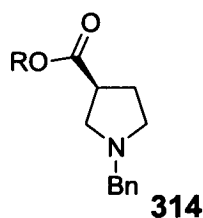
To a solution of *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine (**145**) (0.020 g, 0.084 mmol) and (-)-8-phenylmenthol acrylate (0.020 g, 0.070 mmol) in CH₂Cl₂ (5 mL) was added 3 μL of TFA and the reaction was stirred for 16h. CH₂Cl₂ (10 mL) was added and the organic layer washed with water (3 x 5 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica with a gradient elution of neat CH₂Cl₂, 50% ethyl acetate in hexanes then CH₂Cl₂/MeOH/NH₃

(80:19:1) to yield 23 mg of a 1:1 mixture of diastereomers **314** and **314a** as a clear oil (>95%).

^1H δ : 0.88 (d, $J = 6.5$ Hz, 3H), 1.05 – 1.14 (m, 2H), 1.17 (s, 3H), 1.28 (s, 3H), 1.37 – 1.54 (m, 2H), 1.61 – 1.86 (m, 3H), 1.88 – 2.15 (m, 2H), 2.18 – 2.27 (m, 2H), 2.32 – 2.53 (m, 2H), 2.79 – 2.98 (m, 2H), 3.79 (s, 2H), 4.77 – 4.92 (m, 1H), 7.05 – 7.40 (m, 10H).

^{13}C δ : 21.82 (both), 23.32 (minor), 23.85 (major), 26.31 (minor), 26.41 (major), 26.60 (both), 28.01 (both), 29.01 (major), 29.39 (minor), 31.30 (both), 34.45 (minor), 34.48 (major), 39.48 (minor), 39.53 (major), 41.28 (minor), 41.55 (major), 41.63 (minor), 41.66 (major), 50.08 (major), 50.13 (minor), 52.72 (minor), 53.13 (major), 54.33 (minor), 55.33 (major), 59.09 (major), 59.12 (minor), 74.87 (minor), 75.05 (major), 125.18 (minor), 125.28 (both), 125.31 (major), 127.93 (minor), 127.95 (major), 128.25 (minor), 128.32 (major), 128.76 (major), 128.93 (minor), 129.47 (major), 129.73 (minor), 137.87 (both / only 1 visible), 151.74 (minor), 151.77 (major), 172.86 (major), 172.96 (minor).

(S)-((1R,2S,5R)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-benzylpyrrolidine-3-carboxylate (314)



314 *via* synthesis:

To a solution of *N*-benzylglycine potassium chloride salt (0.047 g, 0.209 mmol) and paraformaldehyde (0.010 g, 0.349 mmol) in toluene (3 mL), was added (-)-8-phenylmenthol

acrylate (0.020 g, 0.070 mmol). The mixture was heated under reflux for 16h under Dean-Stark conditions, then cooled, and saturated ammonium chloride was added (5 mL). The organic layer was separated, and the aqueous extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were washed with water (2 x 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue through a bed of silica with 10% ethyl acetate in hexanes followed by DCM/MeOH/ NH_3 (80:19:1) gave 24 mg of **314** as a clear oil, (>95%).

314 *via* epimerisation:

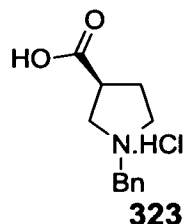
A solution of **314** and **314a** was heated in toluene (3 mL) with a catalytic amount of DBU (5 μL) or KOH (5 mg) for 16h under Dean-Stark conditions. After cooling 5 mL of ethyl acetate was added, and the organic layer was washed with water (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield **314**. (Reflux was shown to be unnecessary to perform the epimerisation with DBU.)

IR: 2954, 2924, 1722, 1645, 1454, 1325, 1198, 1173, 764, 699.

HRMS (APCI): 420.2903, $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{38}\text{NO}_2$ 420.2897.

^1H δ : 0.88 (d, $J = 6.5$ Hz, 3H), 1.05 – 1.14 (m, 2H), 1.17 (s, 3H), 1.28 (s, 3H), 1.37 – 1.54 (m, 2H), 1.61 – 1.86 (m, 3H), 1.88 – 2.15 (m, 2H), 2.18 – 2.27 (m, 2H), 2.32 – 2.53 (m, 2H), 2.79 – 2.98 (m, 2H), 3.79 (s, 2H), 4.81 (ddd, $J_1 = J_2 = 10.4$ Hz, $J_3 = 4.0$ Hz, 1H), 7.05 – 7.40 (m, 10H).

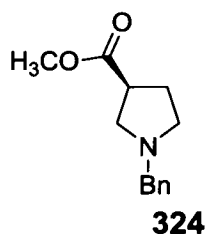
^{13}C δ : 21.96, 24.90, 26.65, 26.77, 28.23, 28.32, 31.39, 34.67, 39.75, 41.79, 42.23, 50.40, 53.98, 56.10, 60.09, 74.40, 125.17, 125.43, 127.96, 128.33, 128.80, 129.15, 139.13, 151.75, 174.42.

(S)-1-Benzylpyrrolidine-3-carboxylic acid hydrochloride (323)

A solution of (*S*)-((1*S*,2*R*,5*S*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 1-benzylpyrrolidine-3-carboxylate (0.231 g, 0.551 mmol) was heated under reflux in 6M HCl (15 mL) for 4h before being cooled and washed with ethyl acetate (3 x 5 mL). Concentration of the aqueous layer yielded 76 mg of **323** as a clear oil (57%).

^1H δ (D_2O): 2.12 – 2.51 (m, 2H), 3.16 – 3.70 (m, 5H), 4.34 (s, 2H), 7.37 – 7.50 (m, 5H).

^{13}C δ (D_2O): 29.30, 29.57, 43.31, 43.59, 55.71, 56.37, 57.08, 60.88, 60.96, 132.07, 132.79, 133.04, 133.10, 178.20, 178.28.

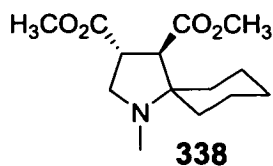
(S)-Methyl-1-benzylpyrrolidine-3-carboxylate (324)

To a solution of (*S*)-1-Benzylpyrrolidine-3-carboxylic acid hydrochloride (0.076 mg, 0.314 mmol) in methanol (5 mL) was added thionyl chloride (0.069 mL, 0.943 mmol). The reaction was stirred for 16 h, before evaporation. Saturated sodium bicarbonate was added (6 mL) then extracted with ethyl acetate (3 x 5 mL), dried (Na_2SO_4) and concentrated to yield 40 mg of amino ester **324** (58%).

^1H δ : 2.07 – 2.14 (m, 2H), 2.49 – 2.58 (m, 1H), 2.61 – 2.79 (m, 2H), 2.90 – 2.96 (m, 1H), 2.98 – 3.10 (m, 1H), 3.65 (s, 2H), 3.67 (s, 3H), 7.18 – 7.36 (m, 5H).

^{13}C δ : 27.68, 41.94, 51.96, 53.71, 56.57, 60.04, 127.24, 128.39, 128.94, 138.30, 175.42.

(±)-(3*R*,4*R*)-Dimethyl 1-methyl-1-azaspiro[4.5]decane-3,4-dicarboxylate (338**)**



To a suspension of sarcosine (0.0958 g, 1.075 mmol) in toluene (5 mL) was added dimethyl fumarate (0.077 g, 0.538 mmol) and cyclohexanone (0.056 mL, 0.538 mmol). The reaction was heated under Dean-Stark conditions for 16h, before being cooled. Ethyl acetate was added (5 mL) and the organic layers were washed with saturated aqueous ammonium chloride (2 x 5 mL) and dried (Na_2SO_4). The dried organic layers were filtered through a bed of silica gel, and washed through with neat ethyl acetate (8 mL). Concentration *in vacuo*, followed by sublimation of unreacted dimethyl fumarate yielded 84 mg of **338** as clear oil (60%).

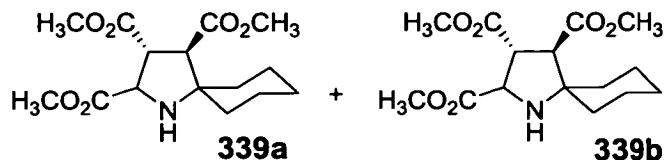
MS (EI) m/z : 269(19%, M^+), 238 (16), 226(96), 210(62), 194(100), 178(12), 166 (70), 154 (26), 94 (28).

HRMS-EI m/z : 269.16253 [M] $^+$ calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_4$; 269.16271.

IR: 2936, 2856, 1734, 1437, 1298, 1254, 1201, 1169, 1023.

^1H δ : 1.16 – 1.67 (m, 10H), 2.24 (s, 3H), 2.84 (dd, $J_1 = 10.5$ Hz, $J_2 = 7.4$ Hz, 1H), 3.16 (d, $J = 7.1$ Hz, 1H), 3.30 (dd, $J_1 = 10.5$ Hz, $J_2 = 9.2$ Hz, 1H), 3.46 (ddd, $J_1 = 9.2$ Hz, $J_2 = 7.4$ Hz, $J_3 = 7.1$ Hz, 1H), 3.64 (s, 3H), 3.66 (s, 3H).

^{13}C δ : 22.77, 22.82, 25.75, 30.56, 30.88, 35.36, 45.39, 51.84, 52.15, 54.23, 55.57, 67.58, 174.11, 174.48.

(±)-Trimethyl 1-azaspiro[4.5]decane-2,3,4-tricarboxylate (339a + 339b)

To a suspension of 1.023 g (8.17 mmol) of glycine methyl ester hydrochloride in toluene (25 mL) was added 1.14 mL of triethylamine (8.17 mmol). The mixture was stirred for 10 min before 0.705 mL of cyclohexanone was added (6.81 mmol). This was followed by 0.981 g of dimethyl fumarate (6.81 mmol) then the mixture was heated under reflux for 16hr under dean-stark conditions. The reaction was then washed with water, dried Na_2SO_4 and concentrated under reduced pressure. Column chromatography eluting with 20% ethyl acetate in hexanes then 100% ethyl acetate gave 1.362 g of diastereomeric spirocycles **339a** and **339b** in a ratio of 25:1 (71% yield based on recovered dimethyl fumarate).

IR: 734, 915, 1019, 1174, 1224, 1436, 1729(C=O), 1738(C=O), 2935, 2999, 3349 (NH).

MS (EI) m/z : 313(8%, M^+), 254 (44), 238(66), 210(58), 194(100), 178(31), 138 (34), 80 (33).

HRMS-EI m/z : 313.15262 [M] $^+$ calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_6$: 313.15254.

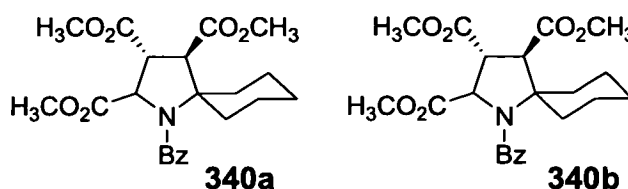
^1H δ : 1.12 – 1.26 (m, 2H), 1.38 – 1.62 (m, 8H), 2.30 – 2.40 (bs, 1H), 2.97 (d, J = 8.1 Hz, 1H), 3.57 – 3.67 (m, 1H), 3.68 – 3.69 (m, 6H), 3.74 (s, 3H), 4.09 (d, J = 8.1 Hz, 1H).

^{13}C δ : 22.28(CH_2), 22.87(CH_2), 25.51(CH_2), 33.33(CH_2), 37.53(CH_2), 51.06 (CH), 52.05 (CH_3), 52.57 (CH_3), 52.64 (CH_3), 58.69 (CH), 61.43 (CH), 65.88 (C), 172.32 (C=O), 173.01 (C=O), 173.36 (C=O).

Minor Diastereomer:

^{13}C δ : 21.89, 22.39, 25.63, 32.52, 38.10, 50.05, 52.30, 52.48, 58.22, 60.81, 64.81, 4 carbons missing or overlapped.

(\pm) Trimethyl 1-benzoyl-1-azaspiro[4.5]decane-2,3,4-tricarboxylate (340a** + **340b**)**



To a solution of (\pm)-trimethyl 1-azaspiro[4.5]decane-2,3,4-tricarboxylate (0.665 g, 2.123 mmol) in dry dichloromethane (30 mL), was added triethylamine (444 μL , 3.18 mmol). This solution was cooled to 0°C and then benzoyl chloride (247 μL , 2.123 mmol) was added dropwise. The reaction was allowed to warm to room temperature and was stirred for 16h before it was quenched with water (5mL), washed with 0.1M hydrochloric acid (2 x 15 mL), followed by 1M sodium hydrogen carbonate (2 x 15 mL), dried and condensed under reduced pressure. Column chromatography eluting with 10% ethyl acetate in hexanes gave 0.8353 g of a 25:1 mix of *N*-benzoyl diastereomers **340a** and **340b** (94% yield).

IR: 702, 736, 914, 1011, 1208, 1247, 1373, 1635, 1729 (C=O), 2952.

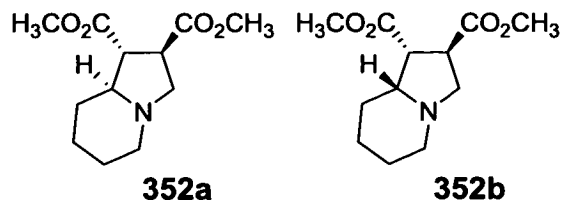
MS (EI) m/z : 417(4%, M^+), 358 (6), 312 (20), 280(5), 105 (100), 77 (13).

HRMS-EI m/z : 417.17831 [M] $^+$ calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_7$: 417.17875.

^1H δ : 1.14 – 1.86 (m, 10H), 2.88 – 3.02 (m, 2H), 3.54 (s, 3H), 3.67 (s, 3H), 3.74 (s, 3H), 4.95 – 4.96 (m, 1H), 7.28 – 7.33 (m, 5H).

^{13}C δ : 23.159 (CH₂), 23.781 (CH₂), 24.351 (CH₂), 29.385 (CH₂), 34.169 (CH₂), 49.036, 52.149, 52.506, 53.068, 54.897, 64.039, 70.304, 126.241, 128.306, 128.618, 129.172, 138.549, 170.850, 170.933, 171.503, 172.383.

**(±)-(1*R*,2*R*,8*aS*)-Dimethyl octahydroindolizine-1,2-dicarboxylate / (±)-(1*R*,2*R*,8*aR*)-
dimethyl octahydroindolizine-1,2-dicarboxylate (352a + 352b)**



To a solution of pipecolic acid (0.062 g, 0.480 mmol), and paraformaldehyde (0.072 mg, 2.40 mmol) in toluene (5 mL) was added dimethyl fumarate (0.080 g, 0.555 mmol). The mixture was heated under reflux under Dean-Stark conditions for 16h, before being cooled. To the cooled solution was added 10 mL of saturated ammonium chloride solution and the organic layer separated. Extraction of the aqueous layer with (2 x 5 mL) ethyl acetate, was followed by combining of the organic layers which were washed with water (1 x 5mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue through a bed of silica gel with 50% ethyl acetate / hexanes gave 80 mg of a 1:1 mixture of **352a** and **352b** (69%).

IR: 2949, 2792, 1735, 1437, 1198, 1172, 999.

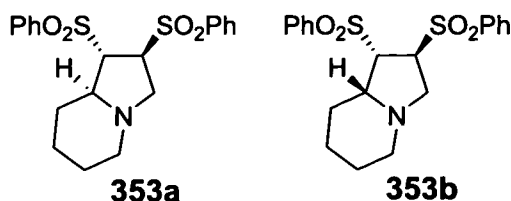
MS (EI) *m/z*: 241(54%, M^+), 226 (76), 210 (75), 182(100), 122 (22), 97 (80).

HRMS-EI *m/z*: 241.13126 [M] $^+$ calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_4$: 241.13141.

^1H δ : 0.94 – 1.61 (m, 8H), 1.70 – 1.82 (m, 3H), 1.86 – 1.99 (m, 4H), 2.13 – 2.29 (m, 3H), 2.45 (dd, $J_1 = J_2 = 9.4$ Hz, 1H), 2.99 (dd, $J_1 = 9.7$ Hz, $J_2 = 6.8$ Hz, 1H), 3.06 – 3.12 (m, 1H), 3.22 – 3.44 (m, 4H), 3.49 – 3.59 (m, 1H), 3.66 (s, 3H), 3.67 (s, 3H), 3.68 (s, 3H), 3.69 (s, 3H).

^{13}C δ : 23.93, 24.26, 24.78, 24.92, 28.04, 30.25, 43.75, 43.86, 49.63, 52.08, 52.20, 52.31, 52.35, 52.55, 52.81, 53.14, 56.60, 57.50, 66.48, 67.91, 173.47, 173.71, 174.10, 174.45, 2 carbons missing or overlapped.

(±)-(1*S*,2*S*,8*aS*)-1,2-Bis(phenylsulfonyl)octahydroindolizine / (±)-(1*S*,2*S*,8*aR*)-1,2-bis(phenylsulfonyl)octahydroindolizine (353a + 353b)



To a solution of pipercolinic acid (0.050 g, 0.386 mmol), and paraformaldehyde (0.019 mg, 0.644 mmol) in toluene (3 mL) was added *trans*-1,2-bis-phenylsulfonyl ethylene (0.040 g, 0.129 mmol). The mixture was heated under reflux under Dean-Stark conditions for 16h, before being cooled. To the cooled solution was added 10 mL of saturated ammonium chloride solution and the organic layer separated. Extraction of the aqueous layer with (2 x 5 mL) ethyl acetate, was followed by combining of the organic layers which were washed with water (1 x 5mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification of the residue *via* flash chromatography on silica gel using a gradient elution with 40% ethyl acetate / hexanes followed by 50%, then neat ethyl acetate gave 15 mg of **353a** (29%), 12 mg of **353b** (23%) and 8 mg of a mixture of **353a** and **353b** (15%).

1st diastereomer

IR: 2940, 1448, 1309, 1150, 1084, 728, 689.

MS (EI) *m/z*: 405(1%, M⁺), 264 (18), 134(19), 122(100), 80(7).

HRMS-EI *m/z*: 405.10529 [M]⁺ calcd for C₂₀H₂₃NO₄S₂: 405.10685.

¹H δ: 0.95 – 1.35 (m, 3H), 1.44 – 1.52 (m, 1H), 1.56 – 1.68 (m, 2H), 1.94 – 2.08 (m, 1H), 2.48 – 2.70 (m, 2H), 2.85 (d, *J* = 10.1 Hz, 1H), 3.38 (d, *J* = 11.1 Hz, 1H), 3.67 – 3.93 (m, 2H), 7.46 – 7.78 (m, 8H), 7.88 – 7.97 (m, 2H).

¹³C δ: 23.76, 24.38, 30.56, 51.75, 54.91, 63.91, 64.34, 68.39, 129.06, 129.23, 129.27, 129.75, 134.29, 134.75, 137.94, 138.01.

2nd Diastereomer

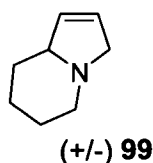
IR: 2949, 1448, 1309, 1150, 1084, 737, 689.

MS (EI) m/z : 405(2%, M^+), 264 (68), 122(100).

HRMS-EI m/z : 405.10577 [M]⁺ calcd for $C_{20}H_{23}NO_4S_2$: 405.10685.

¹H δ : 1.06 – 1.29 (m, 1H), 1.45 – 1.69 (m, 2H), 1.76 – 1.87 (m, 2H), 1.92 – 2.09 (m, 2H), 2.53 (ddd, $J_1 = 11.1$ Hz, $J_2 = 6.4$ Hz, $J_3 = 2.1$ Hz, 1H), 2.62 (dd, $J_1 = 9.5$ Hz, $J_2 = 7.8$ Hz, 1H), 3.08 – 3.18 (m, 1H), 3.29 (dd, $J_1 = 9.5$ Hz, $J_2 = 8.8$ Hz, 1H), 3.98 – 4.14 (m, 2H), 7.49 – 7.82 (m, 10H).

¹³C δ : 24.43, 24.78, 27.39, 54.09, 54.43, 61.60, 66.30, 66.73, 128.67, 129.15, 129.45, 129.76, 134.28, 134.62, 137.70, 138.88.

(±)-3,5,6,7,8,8a-Hexahydroindolizidine

To a solution of **353a** and **353b** (0.030 g, 0.074 mmol) in methanol (2 mL) was added acid washed magnesium turnings (0.036 g, 1.480 mmol) and mercuric chloride (1 mg). The mixture was sonicated for 2h before 2M sodium carbonate was added (5 mL). The mixture was extracted with CH_2Cl_2 (4 x 4 mL) and dried (Na_2SO_4). After filtration 1 drop of conc. HCl was added to the extracts, and the mixture concentrated under reduced pressure to give 9 mg of a clear oil of **99** as its hydrochloride salt (76%). (The NMR data of the free amine **99** in $CDCl_3$ was obtained by performing an *in situ* separation from the hydrochloride salt in D_2O with potassium carbonate.)

¹H δ : 1.30 (m, 2H), 1.57 (m, 2H), 1.80 (m, 2H), 2.48 (m, 1H), 3.00 (m, 2H), 3.15 (dd, $J_1 = 12$ Hz, $J_2 = 6$ Hz, 1H), 3.58 (m, 1H), 5.84 (m, 2H).

¹³C δ : 24.1, 24.7, 29.4, 49.9, 57.5, 67.3, 128.1, 133.6.

Chapter 4: References

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